A STATISTICAL MODEL FOR
THE DIAGNOSIS OF NEONATAL HEART DISEASE

DENNIS MARSHALL FISHER

1976
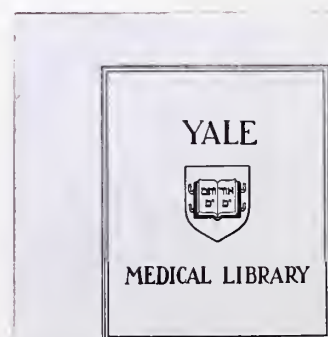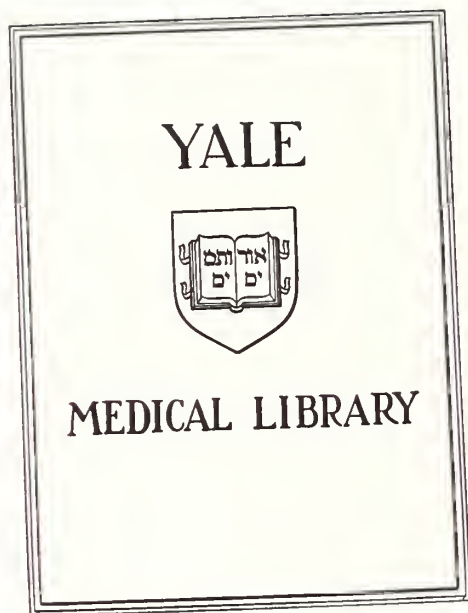
A STATISTICAL MODEL FOR

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A thesis submitted to the faculty of
Pediatrics, Yale University School of
Medicine, in partial fufillment of the
requirements for the degree of Doctor
of Medicine.

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MARCH, 1976

NEW HAVEN, CONNECTICUT

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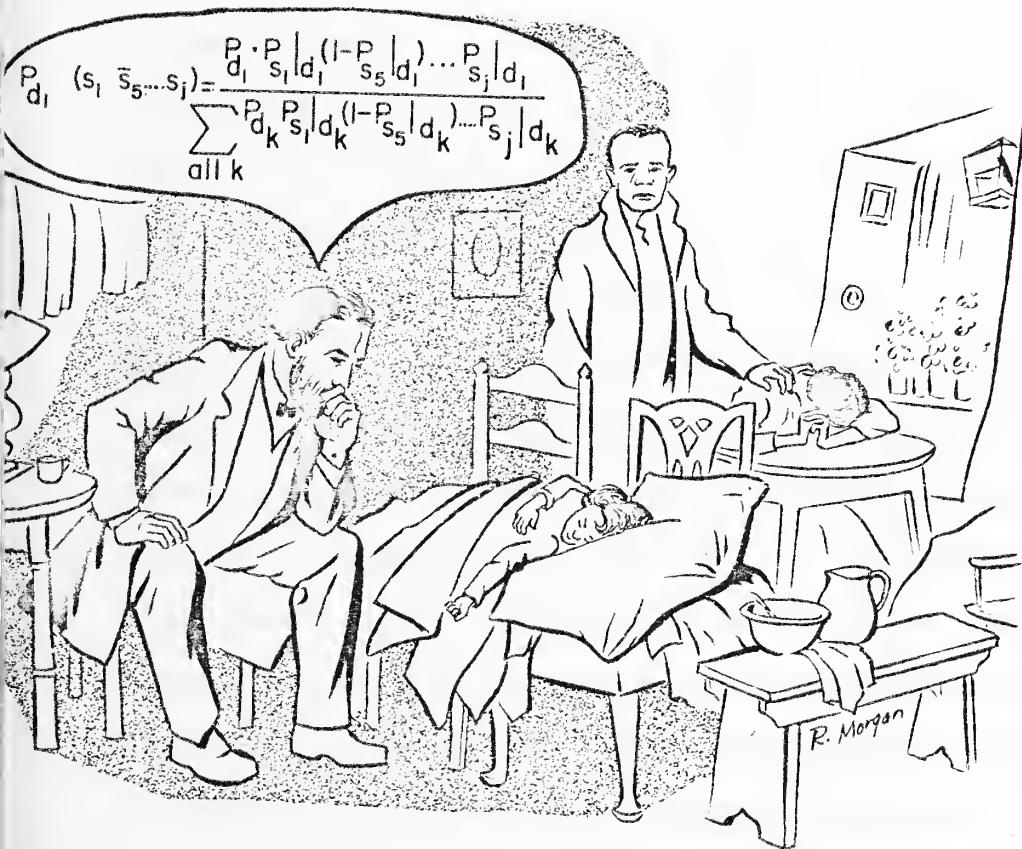
Date 4/14/76

FIG. 1. Bayes' theorem in practice.

From: Lodwick, Gwilym, et al., "Computer Aided Diagnosis
of Radiographic Images" Journal of Chronic Diseases
(Volume 19, No. 4, April, 1966) p. 486.

ABSTRACT

During the last three decades, numerous authors
have attempted to simulate the process through which
clinicians make diagnoses. Limited originally to simple
mechanical models[1,2], the advent of electronic computers
created new technologies[3]. With the introduction of
Boolean Algebra[4], it became possible to apply Bayes Law
(a formula which allows predictions of disease probabil-
ities from incidence data and the occurrence of symptoms
within diseases) to clinical problems.

Studies in the radiographic diagnosis of primary
bone tumors[5], the acute abdomen[6], thyroid disease[7] and
Cushing's syndrome[8] have demonstrated the value of
Bayesian models. Warner et al.[9] studied congenital heart
disease in a population ranging from one month to greater
than twenty years. Their work omitted the neonatal
population, the age during which the most serious cardiac
malformations manifest. This study applies the technique
of Bayesian analysis to a neonatal population. The model
involves identification of the important symptoms (historical,
physical findings, EKG, roentgenographic findings) and
diseases followed by completion of a symptom-disease matrix
(the incidence of each disease as well as the incidence of
each symptom within each disease). Using a computer to
tabulate the enormous quantities of data, the program's
accuracy ranges from fifty-two to sixty percent in different

populations, compared to an approximate clinical accuracy of eighty percent. With variations in the symptom-disease matrix to correct errors in the data, the accuracy of the computer program can be increased to seventy-five percent. In addition, the computer compiles a differential which not only resembles the clinical differential but at times is considered more complete or logical.

With improvements in the data base, it is expected that the program's accuracy can be greatly increased, and could become an effective adjunct to clinical diagnosis. Other studies have demonstrated the utility of Bayesian models as clinical[10] and teaching aids[11]. The possibilities, including simulation of complex clinical problems[12,13], are considerable. As more models are developed, the limiting factor will be physicians' acceptance of computer-based statistical models.

FOOTNOTES

1. F. A. Nash, "Differential Diagnosis" The Lancet
    (Volume 22, No. 6816, April 17, 1954) pp. 874-875.

2. Martin Lipkin, James Hardy, "Differential Diagnosis
    of Hematological Diseases Aided by Mechanical
    Correlation of Data" Science (Volume 125,
    March 22, 1957) pp. 551-552.

3. Lewis Barness, et al., "Computer-Assisted Diagnosis
    in Pediatrics" American Journal of Diseases of
    Children (Volume 127, June, 1974) pp. 852-858.

4. Robert Ledley, Lee Lusted "Reasoning Foundations of
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    July 3, 1959) pp. 9-21.

5. Gwilym Lodwick, et al., "Computer Diagnosis of
    Primary Bone Tumors" Radiology (Volume 80,
    February, 1963) pp. 273-375.

6. J. C. Horrocks, et al., "Computer-Aided Diagnosis"
    British Medical Journal (April 1, 1972) pp. 5-9.

7. Lawrence Fitzgerald, et al., "A Computer Program for
    the Diagnosis of Thyroid Disease" American Journal
    of Roentgenology (Volume 97, No. 4, August, 1966)
    pp. 901-905.

8. C.A. Nugent, et al., "Probability Theory in the Diagnosis
    of Cushing's Syndrome" Journal of Clinical Endo-
    crinology (Volume 24, No. 7, 1964) pp. 621-627.

9. Homer Warner, et al., "A Mathematical Approach to Medical
    Diagnosis" Journal of the AMA (Volume 177, No. 3,
    July 22, 1961) pp. 558-567.

10. E. T. deDombal, "Surgical Diagnosis Assisted by a Computer"
    Proceedings of the Royal Society of London (Volume 184,
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11. J. C. Horrocks, et al., "Production of Artificial Case
    Histories" British Medical Journal (June 5, 1971)
    pp. 578-581.

12. Anthony Gorry, et al., "Sequential Diagnosis by Computer"
    Journal of the AMA (Volume 205, No. 12, September 16,
    1968) pp. 849-854.

13. A. S. Ginsberg, Decision Analysis in Clinical Patient
    Management with an Application to the Pleural
    Effusion Syndrome (Santa Monica, Rand Corporation,1971)

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CONTENTS

CHAPTER I

The process by which the practitioner of medicine formulates clinical decisions is complicated. In its simplest form, it can be seen as having three components. First, the clinician interacts with the patient to make observations and accumulate data. This is in the form of obtaining a history, performing a physical examination and ordering the appropriate laboratory procedures. Second, the clinician takes the information he has gathered and translates it into a diagnosis, an assessment of the disease process with which the patient presents. Finally, the clinician formulates a plan of therapy which reflects both the illness and the opportunities for intervention through medical care, social or possibly economic change.

To aid the clinician in learning the first of these tasks, there are many resources. Early in medical training, he is exposed to a course in physical diagnosis. Numerous textbooks offer the trainee techniques of examination. During clinical training, through constant exposure and experimentation, the student is able to secure an adequate knowledge of physical diagnosis.

To formulate a plan of therapy, the clinician is again offered a large number of resources. Medical

literature abounds with textbooks and journals, and faculty and housestaff are available to help with clinical problems. Having identified the disease under consideration, the physician need only turn to these sources to obtain information about a clinical problem.

It is the middle component - the translation of data into diagnosis - that challenges the trainee. Often, the diagnosis is readily apparent from the history, physical findings or laboratory data. A student, examining a patient with the recent onset of fever, sputum-productive cough and an infiltrate on chest roentgenogram, need not have great insight to suspect the presence of a pneumonia. Frequently, however, the diagnosis is more complicated, either from the difficulty of obtaining sufficient historical, physical examination or laboratory data, variation of the patient from the classical case or the spectrum of presentations of the same disease.

Senior clinicians, when asked to explain their diagnostic reasoning, may employ the term "clinical judgment". This implies, "I recognize something in this patient which clues me towards a specific diagnosis". In identifying their decision process, some invoke the presence of an obscure finding, others may describe a patient with a similar presentation they saw at some other time in their career. Astute clinicians are often

able to outline their decision processes, making explicit
the manner in which they accumulate and process data.
An anecdote offered by Mack Lipkin, a psychiatrist with
an interest in early medical training, describes an
interesting example:

> When first seen, the patient aged seventy, was
> lying on his back in a dimly lit room literally
> screaming because of violent abdominal pain. Only
> two things were instantly apparent to the other
> physician and me - enormous abdominal distension
> and extreme generalized abdominal tenderness. The
> history and further examination showed that the
> patient had peritonitis of unknown origin. He
> had been ill for four days but had refused to call
> a physician. He did not remember where the pain
> began or whether he had had a bowel movement. When
> the surgeon arrived, he was given the information:
> four days of pain, obvious peritonitis, and a temp-
> erature of 105 degrees Fahrenheit. He walked into
> the patient's bedroom, took one look, and in about
> five seconds, said, "Ruptured retrocecal appendix."
> Asked why he was so sure that the offending organ
> was the appendix, that it was ruptured, and that it
> was retrocecal, he looked surprised. He said, "What
> else can it be? Look where he has burned himself
> with his hot water bottle." The other physician and
> I looked at the abdomen which had the reticulated
> pattern that results from continued use of the heating
> pad, stared at each other, and then turned to the
> surgeon. "Why do heating pad burns mean a ruptured
> retrocecal appendix?" He answered, "But look where
> the marks are darkest." We looked carefully and could
> see no difference. He pointed to the extreme right
> side of the abdomen. We looked again and agreed that
> perhaps these marks were slightly darker. He explained
> that he knew of no other condition that would start
> with pain in that part of the extreme right side of
> the abdomen and go on to produce peritonitis except
> a ruptured retrocecal appendix. His diagnosis was
> absolutely correct.[1]

Rarely is the clinician called upon to make such difficult
observations. Nonetheless, he often makes diagnoses
without having made specific observations on all aspects

of the patient or making explicit statements regarding his observations.

During the last three decades, the process by which clinicians make diagnoses has come under careful scrutiny. Initially, theoreticians attempted to build simple mechanical models to aid in the teaching of certain diagnostic problems. In the nineteen fifties, Boolean algebra and logic, with their ability to translate language into mathematical or logical statements, offered researchers the opportunity to simulate simple clinical models. With the development of high speed electronic computers with their massive storage capacities, some authors have simulated more complex clinical situations.

The purpose of this dissertation is three-fold. First the author will review the history of these diagnostic models. Then, a clinical model which has been developed and tested for use in the diagnosis of congenital heart disease in the newborn period will be presented. Finally, there will be a discussion of the implications of these diagnostic models in present-day clinical medicine, as well as some of the opportunities for future research and clinical application.

FOOTNOTES

1.   Mack Lipkin, <u>The Case of Patients</u> (New York, Oxford
      University Press, 1974) pp. 155-156.

FOOTNOTES

1. MacLipkin, The Case of Patients (New York, Oxford University Press, 1974) pp. 155-156.

THE LITERATURE

Confronted with each new medical problem, the physician begins by recalling recognized patterns of disease. To systematize his thinking, although not necessarily consciously, he calls into action an algorithm, a procedure for solving a problem.

The simplest algorithm - one symptom or some combination of symptoms or signs stimulating the physi-cain towards a particular diagnosis or category of diagnoses - can be represented symbolically as:

$$Symptom(s) \longrightarrow Disease(s)$$

To further this process, the clinician may call upon a textbook of differential diagnosis, a resource structured similarly to the algorithm shown above. Considering each of the symptoms separately, the physician compiles lists which may overlap partially, completely, or not at all. Extracting the common elements, he is often able to make a significantly smaller list, and if addi-tional data is made available, the list of diagnostic possibilities can be limited even further. Through this process, the clinician has extended the linear model shown above to a more complex one, a model

which involves the intersection of different sets.

A Mechanical Model

If the number of symptoms is extensive, the text-
book of differential diagnosis comprehensive, or more
than one disease present, the clinician may have created
an enormous task, the culling and sorting of hundreds
of different diseases before the appropriate diagnosis
can be entertained. To simplify this task, Nash[1] out-
ined in 1954 a tool which he felt could be beneficial
for medical diagnosis. The device, which viewed on side
resembles a large slide rule, consists of a frame into
which a number of different strips can be inserted
(Figure 1). Into one edge of the frame, disease names
are inscribed (three hundred in this case, but limited
only by space). The strips, each of which represents
data obtained from history, physical examination or labor-
atory procedures, are slipped into the frame, one beside
the other. Markings on the "symptom" strips then line
up adjacent to the diseases in which they are present.
By selecting strips to represent the patient's symptoms
and observing the frame for the location of the greatest
number of markers, the clinician is able to simplify his
differential diagnosis.

While rather cumbersome, this device is an attempt
to simplify the use of textbooks of differential diagnosis.

ALIGNMENT STOP

FRAME

FRAME

ABORTION
ACHYLIA GASTRICA
ACROMEGALY -
ACTINOMYCOSIS
ADAMS- STOKES SD.
ADDISON'S DISEASE
ALCOHOLISM
ALLERGY
AMOEBIASIS
AMYLOID DISEASE
AMYOT. LAT. SCL.
ANAEMIA HYPOCHROMIC

(DISEASE)
CATEGORY
REFERENCE
INDEX

SLIDABLE CURSOR

FRAME

FRAME

WORMS INTESTINAL
X RADIATION
YAWS
YELLOW FEVER

| 78 | 63 | 122 | 15 | 374 | 16 | 29 |

DETACHABLE (SYMPTOM) MEMBERS
IN POSITION IN FRAME

FIGURE 1

A SIMPLE MECHANICAL MODEL

From: Nash, F. A., :Differential Diagnosis" The Lancet
(Volume 22, No. 6816, April 17, 1954) p. 875.

Proposed before the era of computational devices, it applied the technology of the era.

Early Data Punching

Three years later, as punched cards became available to the scientific community, Lipkin and Hardy[2] utilized the newer technology. They proposed to "evaluate the efficiency with which mechanical classification and correlation of data might assist in the utilization of data in the differential diagnosis of ... disease."[3] Using marginal punched cards (Figure 2), a type of data card in which each hole punched around the edge of the card represents a specific piece of information, one space corresponding to every observation to be considered, they selected 138 findings from history, physical examination, peripheral blood, bone marrow and other laboratory examinations. Twenty-seven hematological diseases were classified according to these criteria and a "master card" prepared for each disease by punching a wedge between the appropriate hole and card edge.

Eighty case records from a university hospital were then abstracted and the appropriate information punched on marginal cards. The cards were tabulated, apparently by comparing each patient card to each of the 27 disease cards. For fifty of the cases an exact correlation to one disease was obtained, and in each it was identical

FIGURE 2

A MARGINAL PUNCHED CARD

to the clinical diagnosis obtained from the hospital
chart. In twenty-three, the data from the case corres-
ponded to more than one of the master cards. For these,
additional data was obtained from the charts and when
retabulated each of the diagnoses was made precisely.
In only seven cases was the data not identical to any
of the master cards. In returning to these medical
records, each patient was found to have more than one
hematological disease.

A year later, Lipkin and Hardy[4] presented a more
sophisticated model using the same data in conjunction
with mechanical techniques. Now using 26 diseases
punched as before, they took advantage of the opportunities
offered by marginal punching, a process termed "direct
sorting"[5]. To find all the diseases characterized by
a single observation, for example, splenomegaly, "one
would place this set of cards front to back and place a
metal or plastic rod into the hole to which that item had
been assigned. When the rod was raised, cards represent-
ing diseases characterized by a large spleen would fall,
because the triangular wedge would have been punched into
that space. Cards without the wedge would be raised"[6].
Discarding the eliminated diagnoses and inserting a rod
corresponding to a second symptom, the number of "eligible"
diagnoses could be further limited. When the symptom
list was exhausted several possibilities could occur:

no disease, only one, or more than one remained in
the differential. As before, in 73 of the 80 cases a
single correct diagnosis was obtained. The elimination
of all possible diagnoses never occurred while in seven
cases, additional mathematical manipulation was necessary
to obtain the diagnosis.

Electronic Models

With the development of high-speed electronic compu-
ters, attempts were made to utilize the newer technologies.
Barness[7] proposed a computer-assisted diagnostic program
which presently include 1,500 different diagnoses. The
patient's symptoms, selected from a comprehensive list
of 650 abnormal findings (75 historical, 315 physical,
60 roentgenographic, and 200 laboratory findings) are
entered via a teletypewriter to a remote computer facility.
"The computer systematically searches its data bank,
comparing the patient's findings with each diagnosis.
The computer selects the diagnoses that should be included
in a complete differential diagnosis. These are listed
in a computer report by the teletypewriter terminal"[8].

To apply the system to clinical situations hospital
records were reviewed to find pediatric patients whose
final diagnosis was not included in the admitting differ-
ential. Twenty charts were abstracted and abnormal

findings selected from the initial history. When
tabulated by the program, for eighteen of the twenty
cases the differential provided by the computer
included the discharge diagnosis. Although the program
is presently extremely expensive - each run costs $50 -
the authors contend that with general use its price
could become "similar with that of a customary laboratory
test"[9] . In addition, the differential diagnosis is
often too long to be clinically useful.

Decision Trees

Alternatively, one can employ decision trees as
diagnostic aids. A typical one, proposed by Krovetz[10]
(Figure 3) offers the user a number of decision nodes
from which to choose. After each selection is made,
he reaches another node, until finally, a minimal number
of diagnoses can satisfy the acknowledged criteria.

Decision trees, while very useful in simple and
"classical" cases, tend to have significant limitations.
Atypical cases, or those which present in varied ways,
tend to become lost in the decision process. For example,
Krovetz's cardiological model uses "obvious cyanosis"
as its first nodal point. Following each of the superior
alternatives - no cyanosis, no thrill, decreased pulmonary
markings - one reaches a point at which no diagnoses are
tenable. The authors then suggest reexamination for
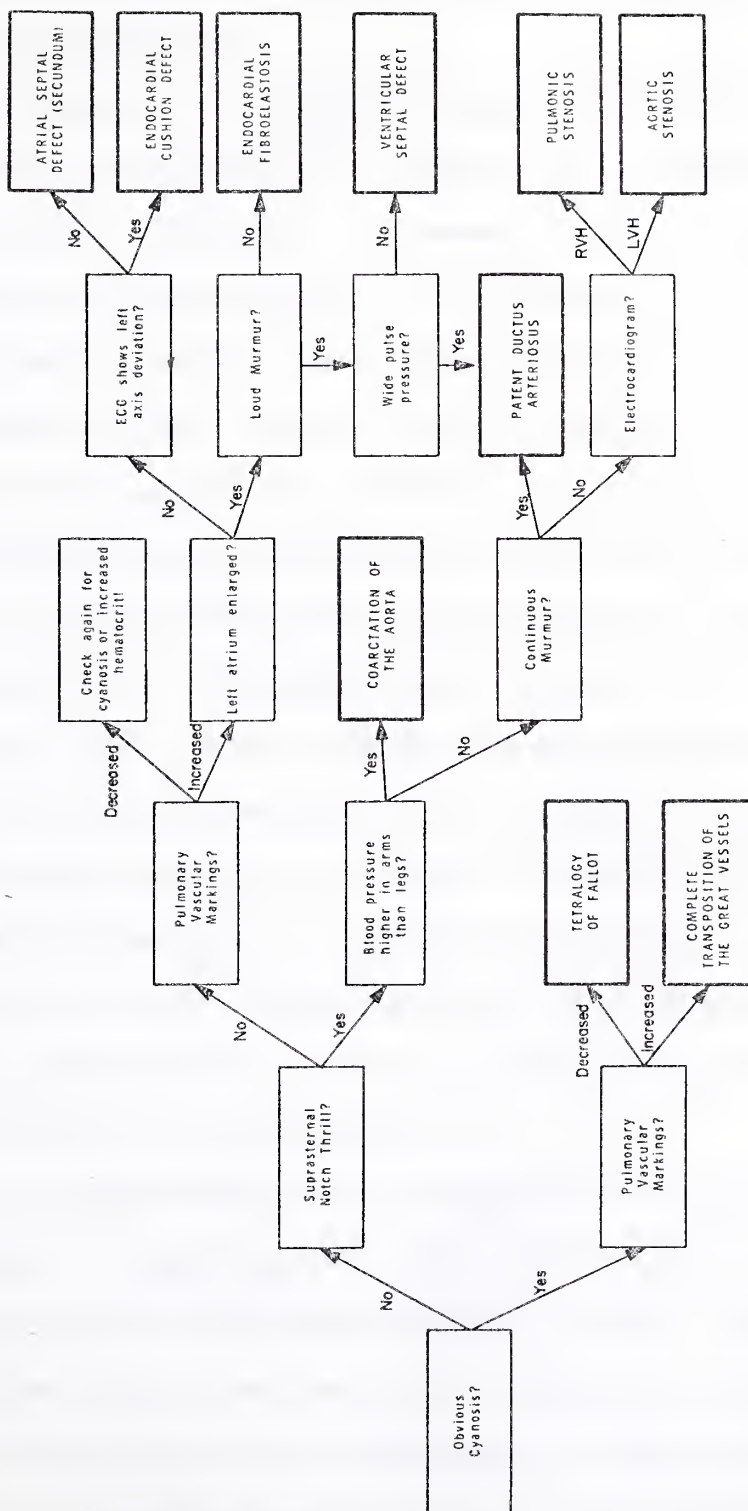
Figure 211. Schema of differential diagnoses after one year of age.

FIGURE 3

A branching sequence for the diagnosis of congenital
heart disease.

cyanosis, allowing for either observer error or varia-
tions in hematocrit.

An attempt to circumvent these limitations was
proposed by Kleinmuntz[11]. His decision tree involves
neurological diagnosis, "an example par excellence of
diagnostic problem solving ... because of the highly
structured nature of the clinical data within it."[12]
The scheme evolves from a game of "Twenty Questions"
in which the experimenter thinks of a disease while the
other participants are invited to ask questions in
pursuit of the diagnosis. The information provided by
the neurologist, characterizing symptoms S1,S2,S3,etc.
(Figure 4) may involve history, physical exam or laboratory
data. Following completion of the game, a diagnostic
tree is built, which is intended "to be an information
processing theory of ... diagnostic behavior.... [The]
program is a theory that explains the diagnostic problem
solving behavior of individual clinical neurologists in
a given set of n situations."[13]

Two distinct models of diagnosis are proposed by
Kleinmuntz. The computer could "have stored in its
memory core all the known symptoms, signs, demographic
variables, laboratory tests and treatments, and then
when a particular set of symptoms or signs are presented
to it, the computer could proceed very much like a
beginning medical student who might consult a diagnostic

Fig. 1. A tree structure of a neurologist's diagnostic game in which the information given was: Sudden left central scotoma and right hemiparesis in a 55 year old.

FIGURE 4

A neurologist's branching sequence.

From: Kleinmuntz, Benjamin, "Diagnostic Problem Solving by Computer" Japanese Psychological Research (Volume 7, No. 4, 1965) p. 192.

manual or textbook."[14]   In addition to being very tedious,
this program would teach very little about the "diag-
nostic process".   Alternatively, the program could
incorporate all the above information "and take into
consideration the relative frequency of a set of symptoms
for a particular disease and the frequency of occur-
rence of a particular disease in a particular geographic
region."[15]

One model employing these techniques appears in a
recent paper by Brand, Dove and Meyers.[16]   To character-
ize the difference between non-bacterial and bacterial
meningitis, they examined the records of several hundred
children seen at the Yale New Haven Hospital during
a fifteen year period.   Several innovations appear in
their study including derivation of "cutoff points"
from data analysis rather than arbitrary criteria, and
use of statistical techniques rather than "clinical
judgment" to determine which criteria discriminate
"best".   Above all, the branching sequence does not
offer only one diagnosis at the completion of all the
nodes but considers at all points the likelihood of
bacterial versus non-bacterial meningitis (Figure 5).
Only if the likelihood were zero or 100% would this
be equivalent to the traditional branching sequence.

COMPLETE PROBABILITY TREE
DISTRIBUTION OF CASES BASED ON COMBINED PATIENT AGE, CSF GRAM STAIN, CSF GLUCOSE LEVEL
AND CSF WHITE CELL COUNT
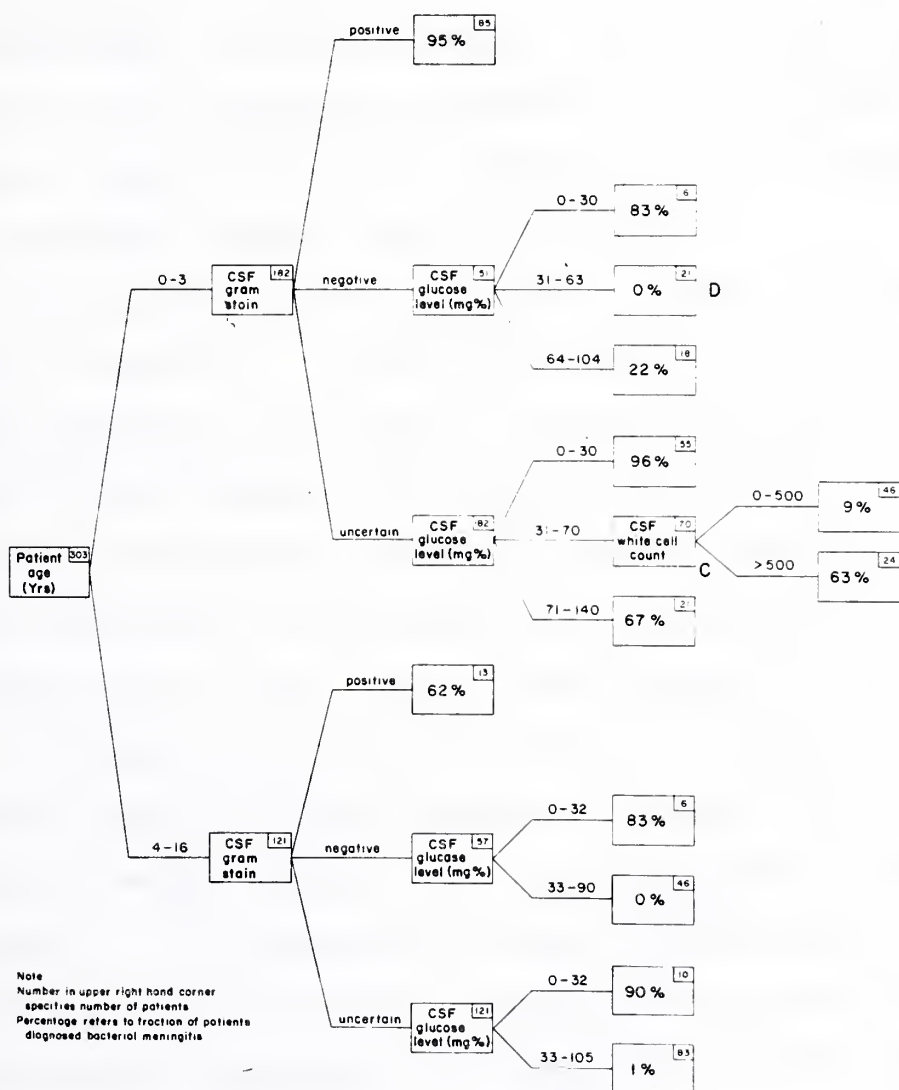
FIGURE 5

A branching sequence for the differentiation of
non-bacterial and bacterial meningitis.

From: Brand, Don, et al., "A Technique for Analyzing
        Clinical Data to Provide Patient Management
        Guidelines: A Study of Meningitis in Children"
        Submitted for publication.

Statistical Models

In 1964, Lipkin[17] proposed a statistical model
to supplement his earlier work. Recognizing that the
marginal card technique was unable to differentiate
between important and less important data, he sought
to weigh the relative value of symptoms.

Using twenty-six hematological diseases, he listed
the 138 symptoms. "A numerical value or weight was
then assigned to each item of information present in
each of the diseases. The instructions stated: given
a disease description, assign a positive weight to data
that contribute to the diagnosis, give a negative weight
to data that do not. Let the significance of the item
in the disease determine the weight.... The sum of
all the weights in each disease will yield the total
positive weight and the total negative weight of the
disease.... By comparing the sum of the weighted
diagnostic criteria of the hospital case to the sum of
the weighted diagnostic criteria of the disease, the
degree of identical fit of hospital case data in each
case was defined."[18]

Figure 6 shows the profile of one disease, followed
by the same profile superimposed on a patient profile,
yielding a Diagnostic Score. The Diagnostic Index is:

$$D.I. \;=\; \Sigma \; X \cdot W \,/\, \Sigma \; W$$
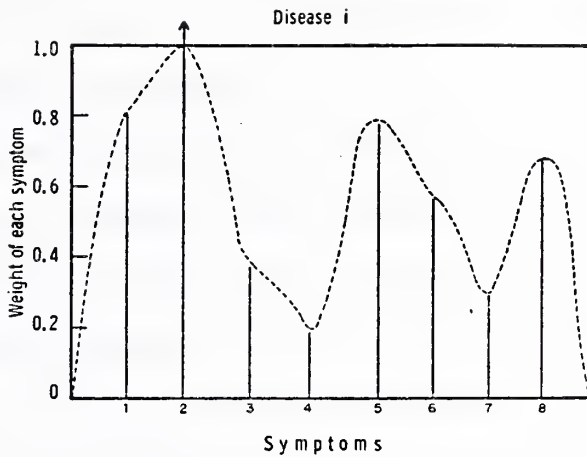
Fig. 2.—Schematic profile of one disease. The abscissa records symptoms 1-8; the ordinate records the weight of each symptom. The dotted line connects the weights and emphasizes groups of symptoms having high and low weights. The arrow defines a pathognomonic symptom.
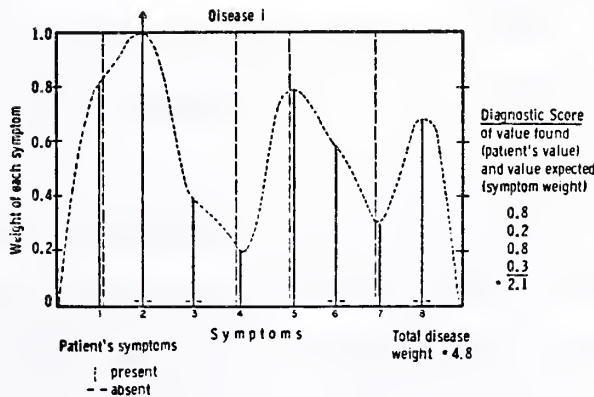
Fig. 3.—The same disease profile (*solid lines*) and the profile of a patient (*dashed lines*) superimposed. The value found (patient's value) is multiplied by the value expected (symptom weight) to produce a Diagnostic Score. Further division by the total disease weight produces the Diagnostic Index. The latter measures *the degree of identical fit* of the patient's data in each disease.

FIGURE 6

From: Lipkin, Martin, "The Likelihood Concept of Differential Diagnosis" Perspectives in Medicine and Biology (Summer, 1964), p. 488-489.

where X (1 or 0) corresponds to the symptom being present or absent. W is the weight assigned to that item in that disease.

"If a hospital case contained all the findings of a given disease, the Diagnostic Index was 1.00. If a hospital case contained none of the findings that characterized a disease, the Diagnostic Index was zero. If it contained one-half the findings of the disease, the Diagnostic Index was 0.5."[19]

Figure 7 demonstrates several representative cases, comparing hospital diagnoses to diagnostic indices. Lipkin notes that "when the Diagnostic Index approached 0.2 the disease in question became important in the differential diagnosis and had many features identical to those in the hospital case. When the Diagnostic Index reached 0.4, the disease was very important".[20]

A second statistical model, for the diagnosis of thyrotoxicosis, was authored by Crooks, Murray and Wayne[21] in 1958. Their method "consisted in allocating a positive or negative score to each clinical feature, the values being based on an analysis of the relative frequency of symptoms and signs in the disease. In this way a total score, or clinical diagnostic index, can be obtained in each case."[22] Signs and symptoms

COMPARISON OF WEIGHTED AVERAGES AND HOSPITAL DIAGNOSES
FOR SEVEN CASES

Case	Diagnostic Index (weighted averages, positive)		Hospital diagnoses
1	Chronic lymphatic leukemia	0.41	Chronic lymphatic leukemia
	Acute hemolytic anemia	0.28	Acquired hemolytic anemia
	Idiopathic thrombocytopenic purpura	0.27	
	Hemophilia	0.26	
2	Agranulocytosis	0.49	Chronic lymphatic leukemia
	Chronic lymphatic leukemia	0.45	Agranulocytosis
	Sprue	0.21	
	Hereditary spherocytosis	0.19	
3	Mediterranean anemia	0.28	Mediterranean anemia
	Hemophilia	0.23	Nonthrombocytopenic purpura
	Acute hemolytic anemia	0.22	
	Multiple myeloma	0.22	
4	Hypochromic microcytic anemia	0.31	Idiopathic thrombocytopenic purpura
	Idiopathic thrombocytopenic purpura	0.27	Anemia, acute and chronic
	Multiple myeloma	0.19	
	Mediterranean anemia	0.15	
5	Multiple myeloma	0.37	Multiple myeloma
	Aplastic anemia	0.34	Agranulocytosis
	Agranulocytosis	0.30	
	Chronic lymphatic leukemia	0.09	
6	Agranulocytosis	0.47	Agranulocytosis
	Chronic lymphatic leukemia	0.21	Macrocytic anemia
	Eosinophilic leukemia	0.19	
	Monocytic leukemia	0.18	
7	Agranulocytosis	0.47	Macrocytic anemia
	Aplastic anemia	0.21	Neutropenia
	Chronic lymphocytic leukemia	0.19	Thrombocytopenia
	Acute posthemorrhagic anemia	0.19	

FIGURE   7

Diagnostic indices for sample hematological cases

were chosen "because they had previously been shown
by a clinical survey to differ in their incidence in
thyrotoxic and normal subjects."[23] Weights were assigned
to the signs such that "the positive or negative values
of these scores were ... allocated on the basis of the
relative diagnostic significance of each"[24] as found in
previous studies (Figure 8). After some modifications
necessary to accomodate for observer variation, the
clinical diagnostic indices were calculated. In a group
of patients who were clinically "non-toxic", the scores
ranged from -16 to +10 while definitely "toxic"
patients ranged from +21 to +42. One hundred eighteen
patients, for whom an initial clinical diagnosis was
unclear despite radioactive iodine studies, were placed
in a "doubtful" group. Of the sixty-seven felt to be
non-toxic by final clinical diagnosis, fifty-nine had
diagnostic indices in the non-toxic range (less than 11),
seven in the intermediate range and one in the toxic
range (twenty or greater). Of these eventually felt
to be toxic, none fell into the non-toxic range, six
in the intermediate area and forty-five had diagnostic
indices which correlated with their clinical status.
Exluding the single non-toxic patient with a toxic
index, these data would suggest that a diagnostic

TABLE I

Weighting Factors Allocated to the Symptoms and Signs of Thyrotoxicosis

Symptoms of recent onset or increased severity	Present (score)	Absent (score)	Signs	Present (score)	Absent (score)
Dyspnoea on effort	+1		Palpable thyroid	+3	−3
Palpitations	+2		Bruit over thyroid	+2	−2
Tiredness	+2		Exophthalmos	+2	
Preference for heat (irrespective of duration)		−5	Lid retraction	+2	
			Lid lag	+1	
Preference for cold	+5		Hyperkinetic movements	+4	−2
Indifferent to temperature	0		Fine finger tremor	+1	
Excessive sweating	+3		Hands:		
Nervousness	+2		Hot	+2	−2
Appetite increased	+3		Moist	+1	−1
Appetite decreased		−3	Casual pulse rate:		
Weight increased		−3	Auricular fibrillation	+4	
Weight decreased	+3		Regular rate:		
			Under 80		−3
			80–90	0	
			Over 90	+3	

FIGURE 8

index of ten or less represented a non-toxic patient while at greater than twenty, hyperthyroidism was present. In the intermediate range, a relatively small group, no conclusions could be drawn.

A third statistical model was proposed by Collen, et al.[25] , for use in the Kaiser Foundation Health Plan. As part of a multiphasic screening program, an attempt was made to identify "whether there is sufficient likelihood of disease being present to warrant further specific diagnostic testing".[26] One example, the differentiation of asthmatic patients from those without asthma, involved a "likelihood" principle proposed by Neyman [27] . The likelihood ratio "is the ratio of the probability (P_D^S) with which a selected set of symptoms (S) occurs in a specific disease (D) to the probability (P_N^S) with which the same set of symptoms (S) occurs in the non-diseased state (N); that is $\theta = P_D^S / P_N^S$. Each symptom set, therefore, is associated with a θ value. The θs are then arranged in order of increasing magnitude." [28]

"Six dichotomous questions were selected from a questionnaire form given to 230 patients with a clinical diagnosis of bronchial asthma and to a group of 517 randomly selected patients who ... were known to be free of asthma."[29] The results, shown in Figure 9 demonstrate an area in which the likelihood is zero and another with a likelihood of infinity. Interestingly, seven percent

Table 2—Proportion of Patients with (P_D^S) and without (P_N^S) Bronchial Asthm[a] Answering Yes to Six Diagnostic Questions

Question Number						Asthma Patients		Nonasthma Patients		Likelihood Ratio
1	2	3	4	5	6	No.	(P_D^S)	No.	(P_N^S)	$\theta = (P_D^S / P_N^S)$
No	No	No	Yes	No	No	0	0	16	0.03095	0
No	No	No	No	Yes	No	0	0	6	0.01161	0
No	No	No	Yes	No	Yes	0	0	20	0.03868	0
No	No	Yes	No	No	Yes	0	0	5	0.00967	0
No	No	Yes	Yes	No	No	0	0	3	0.00580	0
Yes	No	No	Yes	No	No	0	0	3	0.00580	0
Yes	No	No	No	Yes	No	0	0	1	0.00193	0
No	No	No	Yes	Yes	No	0	0	1	0.00193	0
No	No	Yes	Yes	No	Yes	0	0	5	0.00967	0
No	No	No	Yes	Yes	Yes	0	0	2	0.00387	0
Yes	No	No	Yes	No	Yes	0	0	1	0.00193	0
Yes	No	Yes	No	No	Yes	0	0	1	0.00193	0
Yes	No	No	Yes	Yes	No	0	0	1	0.00193	0
No	No	Yes	Yes	Yes	No	0	0	1	0.00193	0
Yes	No	Yes	Yes	Yes	No	0	0	1	0.00193	0
Yes	No	Yes	Yes	No	Yes	0	0	1	0.00193	0
Yes	No	Yes	No	Yes	Yes	0	0	1	0.00193	0
Yes	No	No	Yes	Yes	Yes	0	0	1	0.00193	0
No	No	No	No	No	Yes	1	0.00435	24	0.04642	0.094
No	No	No	No	No	No	16	0.06957	353	0.68279	0.102
No	No	No	No	Yes	Yes	1	0.00435	8	0.01547	0.281
No	No	Yes	No	No	No	5	0.02174	33	0.06383	0.341
Yes	No	No	No	No	No	1	0.00435	5	0.00967	0.500
Yes	No	No	No	Yes	Yes	1	0.00435	1	0.00193	2.25
No	Yes	Yes	No	No	Yes	3	0.01304	2	0.00387	3.37
No	Yes	Yes	Yes	No	No	2	0.00870	1	0.00193	4.50
No	Yes	No	No	No	No	21	0.09130	7	0.01354	6.74
No	Yes	Yes	No	Yes	Yes	3	0.01304	1	0.00193	6.74
No	Yes	Yes	Yes	No	Yes	3	0.01304	1	0.00193	6.74
No	Yes	No	No	No	Yes	11	0.04783	3	0.00580	8.24
Yes	Yes	No	No	No	No	23	0.10000	4	0.00774	12.92
No	Yes	Yes	No	No	No	18	0.07826	2	0.00387	20.23
Yes	Yes	Yes	No	Yes	Yes	11	0.04783	1	0.00193	24.73
Yes	Yes	No	Yes	Yes	Yes	15	0.06522	1	0.00193	33.72
No	Yes	No	No	Yes	No	1	0.00435	0	0	∞
No	Yes	No	Yes	No	No	1	0.00435	0	0	∞
No	No	Yes	No	Yes	Yes	1	0.00435	0	0	∞
No	Yes	Yes	No	Yes	No	1	0.00435	0	0	∞
Yes	Yes	No	No	Yes	No	1	0.00435	0	0	∞
Yes	Yes	No	Yes	No	No	2	0.00870	0	0	∞
Yes	Yes	No	No	No	Yes	3	0.01304	0	0	∞
No	Yes	No	Yes	No	Yes	5	0.02174	0	0	∞
No	Yes	No	No	Yes	Yes	5	0.02174	0	0	∞
Yes	Yes	Yes	No	No	No	14	0.06087	0	0	∞
Yes	Yes	Yes	Yes	No	No	1	0.00435	0	0	∞
Yes	Yes	No	Yes	Yes	No	1	0.00435	0	0	∞
No	Yes	No	Yes	Yes	Yes	1	0.00435	0	0	∞
No	No	Yes	Yes	Yes	Yes	1	0.00435	0	0	∞
Yes	Yes	Yes	No	No	Yes	4	0.01734	0	0	∞
Yes	Yes	No	Yes	No	Yes	5	0.02174	0	0	∞
Yes	Yes	No	No	Yes	Yes	8	0.03478	0	0	∞
Yes	Yes	Yes	Yes	Yes	No	1	0.00435	0	0	∞
Yes	Yes	Yes	Yes	No	Yes	3	0.01304	0	0	∞
No	Yes	Yes	Yes	Yes	Yes	3	0.01304	0	0	∞
Yes	Yes	Yes	Yes	Yes	Yes	33	0.14348	0	0	∞

Note: Nonasthma group total 70 with (P_N^S) subtotal 0.13535. Asthma group total 95 with (P_D^S) subtotal 0.41301.

FIGURE 9

Likelihood ratios for six diagnostic questions.

From: Collen, Morris, et al., "Automated Multiphasic Screening and Diagnosis" American Journal of Public Health (Volume 54, No. 5, May, 1964), p. 746.

of the asthmatics and 68 percent of the non-asthmatics
answered no to all the questions, providing a likelihood
of .102 for that set of responses.

These results were used to select a "positive
region which locates the combination of questions which
screen out as positive the maximum number of patients
with asthma with a low error of false negative."[30]
Recognizing that "for bronchial asthma, an error in
diagnosis may not be of immediate serious consequences,
a relatively high ... [likelihood ration cutoff] for this
test may be selected."[31]

Boolean Algebra

With the development of statistical diagnostic models,
it became apparent that diagnosis lent itself to the
use of algorithms. It was Ledley and Lusted[32] in their
article "Reasoning Foundations of Medical Diagnosis" who
introduced Boolean Logic to medical diagnosis. They
suggested that "the first step in making a logical
analysis of this process is to review some symbolism
associated with the propositional calculus of symbolic
logic. Such symbolism enables the more precise communica-
tion of the concepts involved in logical processes."[33]
Symbols, x,y,z..., were introduced to represent attributes
such as a sign (fever) or disease (pneumonia). Correspond-
ing capital letters were used in statements about these
attributes. "For example, y represents the sentence:

The patient has the attribute y. The negation of this statement, the patient does not have the attribute y, is represented by $\overline{Y}$, where the bar (called negation) over the Y indicates 'not'."[34]

Applying Boolean logic, the statement X·Y, the intersection of the separate statements X and Y, implies that the patient has both the attribute x and the attribute y. The statement X + Y, the union of the statements X and Y, indicates the group which has attribute x, attribute y or both. A third statement, X → Y, represents the logical statement, "If the patient has attribute x, he then has attribute y."

The authors generated three functions:[35]

1. $E(S(1),...,S(n),D(1),...,D(m))$ which represents the relationships between diseases the symptoms that comprise medical knowledge,

2. $G(S(1),...,S(n))$ which represents the symptoms presented by a patient, and

3. $f(D(1),...,D(m))$ which represents the diagnosis as Boolean function of the diseases alone.

"The logical aspect of the medical diagnosis problem is to determine the diseases f such that if medical knowledge E is known, then: if the patient presents symptoms G, he has diseases f. In terms of our symbolic

language, the problem is to determine a Boolean function
f that satisfies the following formula:

$$E \rightarrow (G \rightarrow f)$$

This is the fundamental formula of medical diagnosis."[36]

The difficulty of application of these techniques
to medical diagnosis lies not in the theory but in the
lack of direct association between cause and effect,
or in practical terms, symptom and diagnosis. For
example, in a certain disease, there may be a seventy-
five percent chance of a symptom being present.

> Since "chance" or "probabilities" enter into
> medical knowledge", then chance or probabilities
> enter into the diagnosis itself. At present, it
> may generally be said that specific probabilities
> are rarely known; medical diagnostic textbooks
> rarely give numerical values, although they may
> use words such as "frequently", "very often" and
> "almost always". [37]

> The first step in discussing a probabilistic
> analysis of medical diagnosis is to review some
> definitions and important properties of probabili-
> ties. The concept of total probability is concerned
> with the following question. Suppose we select
> at random from our population of patients one single
> patient: what is the chance or total probability,
> that the patient chosen has certain specified
> attributes $f(x,y,...,z)$? By definition, the total
> probability is the ratio of the number of patients
> that have these attributes to the total number of
> patients from which the random selection is made.
> If the total number of patients is N, and if N(f) is
> the number of these patients with attributes f, then
> the total probability that a patient has attributes f
> is:
>
> $$P(f) = N(f)/N$$

> The conditional probability is analagous to
> the total probability, where the selection is
> made only from that subpopulation of patients
> that have the specified condition.[38]

> The problem now is: Which of these choices is
> most probable - that is, which of the disease
> complexes given by the logical diagnosis function
> f is the patient most likely to have. In terms
> of conditional probabilities, the probabilistic
> aspect of the diagnosis problem is to determine
> the probability that a patient has disease f where
> it is known that the particular patient presents
> symptoms G, that is, the probabilistic aspect of
> medical diagnosis is to evaluate $P(f/G)$ for a
> particular patient.[39]

> The data upon which the evaluation of $P(f/G)$ is
> based must, of course, come from medical know-
> ledge. Such medical knowledge is generally also
> given in the form of conditional probabilities -
> namely, the probability that a patient having (a)
> disease complex will have the symptom complex....
> It is interesting to note that most diagnostic
> textbooks discuss the symptoms associated with
> the disease rather than the reverse, the disease
> associated with a symptom. The question that
> naturally arises at this point is: If medical
> knowledge is in the form $P(G/f)$ that is, probability
> of having the symptoms given the patient having the
> disease, then how can we make the diagnosis $P(f/G)$ -
> that is, the probability of having the disease given
> the patient having the symptoms.[40]

It is here that Bayes Law, a well-known formula
for relating cause and effects in probabilistic terms,
becomes important. A derivation of this law appears in
the following chapter. Let it suffice at present to
state that Bayes Law permits the calculation of the
conditional probability of a disease in a given patient
utilizing only the likelihood of the symptom complex
within each disease.

Bayesian Models

Numerous authors have developed Bayesian models
to assist in medical diagnostic problems. Amongst
the earliest was one proposed by Warner, et al.[41], in
1961. Choosing congenital heart disease, because "the
accuracy of diagnosis ... from clinical symptoms may
be checked by cardiac catheterization and/or findings
at surgery, and because relatively objective clinical
findings may be easily obtained,"[42] they studied a
population ranging in age from one month to over twenty
years. Fifty symptoms felt to be of value in the
diagnosis of these disorders, and thirty-three diseases
were chosen (Figure 10). The symptom-disease matrix
(Figure 11) was completed through three sources:

    1. a review of previously published data

    2. chart reviews of 1035 patients previously
        seen by this group

    3. "estimates based upon the pathologic
        physiology of the defect in the
        case of rare defects in which
        adequate statistics were not avail-
        able"[43]

The authors observed that "it is apparent from our
experience ... that the most probable diagnosis ...
agrees with the actual diagnosis made by physiologic

Table 1.—List of Symptoms to Be Evaluated by Physician

Symptoms

- x_1 = age 1 mo. to 1 yr.
- x_2 = age 1 to 20 yr.
- x_3 = >20 yrs.
- x_4 = cyanosis, mild
- x_5 = cyanosis, severe (with clubbing)
- x_6 = cyanosis, intermittent
- x_7 = cyanosis, differential
- x_8 = squatting
- x_9 = dyspnea
- x_{10} = easy fatigue
- x_{11} = orthopnea
- x_{12} = chest pain
- x_{13} = repeated respiratory infections
- x_{14} = syncope
- x_{15} = systolic murmur loudest at apex
- x_{16} = diastolic murmur loudest at apex
- x_{17} = systolic murmur loudest in left 4th interspace
- x_{18} = diastolic murmur loudest in left 4th interspace
- x_{19} = continuous murmur loudest in left 4th interspace
- x_{20} = systolic murmur with thrill loudest in left 2nd interspace
- x_{21} = systolic murmur without thrill loudest in left 2nd interspace
- x_{22} = diastolic murmur loudest in left 2nd interspace
- x_{23} = continuous murmur loudest in left 2nd interspace
- x_{24} = systolic murmur loudest in right 2nd interspace
- x_{25} = diastolic murmur loudest in right 2nd interspace
- x_{26} = systolic murmur heard best over posterior chest
- x_{27} = continuous murmur heard best over posterior chest
- x_{28} = accentuated 2nd heart sound in left 2nd interspace
- x_{29} = diminished 2nd heart sound in left 2nd interspace
- x_{30} = right ventricular hyperactivity by palpation
- x_{31} = forceful apical thrust
- x_{32} = pulsatile liver
- x_{33} = absent or diminished femoral pulsation
- x_{34} = ECG axis more than 110°
- x_{35} = ECG axis less than 0°
- x_{36} = R wave greater than 1.2 mv in lead V_1
- x_{37} = R' or qR pattern in lead V_1
- x_{38} = R wave greater than 2.0 mv in lead V_6
- x_{39} = T wave in lead V_6 inverted (no digitalis)
- x_{40} = early diastolic murmur loudest at apex
- x_{41} = late diastolic murmur loudest at apex
- x_{42} = holo-systolic murmur loudest in left 4th interspace
- x_{43} = mid-systolic murmur loudest in left 4th interspace
- x_{44} = holo-diastolic murmur loudest in left 4th interspace
- x_{45} = early diastolic murmur loudest in left 4th interspace
- x_{46} = mid-systolic murmur with thrill loudest in 2nd left interspace
- x_{47} = holo-systolic murmur with thrill loudest in 2nd left interspace
- x_{48} = mid-systolic murmur without thrill loudest in 2nd left interspace
- x_{49} = holo-systolic murmur without thrill loudest in 2nd left interspace
- x_{50} = murmur louder than gr 3-6

Table 2.—List of Diseases Included in Differential Diagnosis

Diseases

- y_1 = normal
- y_2 = atrial septal defect without pulmonary stenosis or pulmonary hypertension
- y_3 = atrial septal defect with pulmonary stenosis
- y_4 = atrial septal defect with pulmonary hypertension*
- y_5 = complete endocardial cushion defect (A-V communis)
- y_6 = partial anomalous pulmonary venous connections (without atrial septal defect)
- y_7 = total anomalous pulmonary venous connections (supradiaphragmatic)
- y_8 = tricuspid atresia without transposition
- y_9 = Ebstein's anomaly of tricuspid valve
- y_{10} = ventricular septal defect with valvular pulmonary stenosis
- y_{11} = ventricular septal defect with infundibular stenosis
- y_{12} = pulmonary stenosis, valvular (with or without probe-patent foramen ovale)
- y_{13} = pulmonary stenosis, infundibular (with or without probe-patent foramen ovale)
- y_{14} = pulmonary atresia
- y_{15} = pulmonary artery stenosis (peripheral)
- y_{16} = pulmonary hypertension, isolated
- y_{17} = aortic-pulmonary window
- y_{18} = patent ductus arteriosus without pulmonary hypertension*
- y_{19} = pulmonary arteriovenous fistula
- y_{20} = mitral stenosis
- y_{21} = primary myocardial disease
- y_{22} = anomalous origin of left coronary artery
- y_{23} = aortic valvular stenosis
- y_{24} = subaortic stenosis
- y_{25} = coarctation of aorta
- y_{26} = truncus arteriosus
- y_{27} = transposed great vessels
- y_{28} = corrected transposition
- y_{29} = absent aortic arch
- y_{30} = ventricular septal defect without pulmonary hypertension*
- y_{31} = ventricular septal defect with pulmonary hypertension*
- y_{32} = patent ductus arteriosus with pulmonary hypertension*
- y_{33} = tricuspid atresia with transposition

FIGURE 10

Symptoms and diseases for a Bayesian congenital heart disease-diagnostic model.

From: Warner, Homer, et al., "A Mathematical Approach to Medical Diagnosis" Journal of the American Medical Association (Volume 177, No. 3, July 22, 1961) p. 179.

Symptom-disease matrix (Figure 11). The page consists of a large symptom-disease data matrix with disease rows Y1–Y33, incidence column, and symptom columns X1–X50.

Diseases	Incidence	X1	X2	X3	X4	X5	X6	X7	X8	X9	X10	X11	X12	X13	X14	X15	X16	X17	X18	X19	X20	X21	X22
Y1	0.100	01	49	50	01	00	01	00	01	01	10	03	05	05	03	05	01	70	02	07	01	80	01
Y2	.081	10	50	50	02	01	02	00	01	35	50	05	02	40 — 01		02	02	30	20	02	05	90	02
Y3	.005	30	60	10	20	10	20	00	01	60	70	05	02	10	10	02	02	05	05	02	57	40	01
Y4	.001	10	20	70	30	10	25	00	01	80	90	05	05	15	10	02	02	15	20	02	05	40	20
Y5	.027	20	50	30	15	05	10	00	01	40	50	05	05	30	05	60	15	90	40	02	10	20	10
Y6	.005	10	40	50	01	01	01	00	01	15	20	01	05	05	01	02	02	20	02	02	02	60	05
Y7	.001	20	70	10	65	10	05	00	01	70	80	05	05	20	05	02	02	10	15	10	05	75	05
Y8	.018	50	48	02	30	65	01	00	10	80	90	20	05	15	10	02	05	65	05	05	20	20	02
Y9	.001	10	45	45	22	44	01	00	22	80	80	10	30	15	22	05	25	95	25	05	05	15	02
Y10	.054	40	55	65	25	25	10	00	30	75	90	05	05	10	90	02	02	20	02	05	65	25	02
Y11	.063	10	55	05	30	30	10	00	40	75	90	05	05	10	25	02	02	20	02	05	65	25	02
Y12	.045	20	70	10	01	01	01	00	01	50	65	01	01	01	10	02	02	10	02	05	70	20	02
Y13	.013	20	70	10	01	01	01	00	01	50	65	01	01	01	10	02	02	10	02	02	70	20	02
Y14	.014	90	89	01	10	20	00	00	80	90	99	05	10	05	35	02	02	40	05	05	01	02	02
Y15	.001	05	15	50	01	01	01	00	01	01	01	01	01	01	01	04	01	02	01	01	02	25	02
Y16	.013	30	45	45	01	01	01	00	01	70	95	40	10	10	10	01	01	30	05	01	01	05	30
Y17	.001	30	60	10	05	01	01	00	01	10	10	05	01	10	01	05	10	20	05	60	01	10	05
Y18	.072	20	40	40	01	01	01	00	01	20	20	10	01	10	05	05	15	10	02	50	02	13	05
Y19	.002	20	20	50	45	45	01	00	01	10	20	05	01	01	10	05	02	10	02	20	02	10	02
Y20	.008	20	50	30	01	01	01	00	01	50	50	40	05	10	10	80	20	10	10	02	05	10	02
Y21	.013	70	29	01	01	01	01	00	01	40	50	20	01	05	05	15	02	05	02	02	02	05	02
Y22	.001	70	29	01	01	01	01	00	01	30	30	30	80	15	20	05	01	01	01	01	01	01	01
Y23	.036	10	80	10	01	01	01	00	01	20	30	20	15	01	35	02	20	10	02	05	05	01
Y24	.009	10	80	10	01	01	01	00	01	20	30	20	15	01	35	20	02	20	10	02	05	05	01
Y25	.054	10	70	20	01	01	01	00	01	20	30	20	01	01	05	05	01	20	10	02	02	10	01
Y26	.005	50	40	10	30	60	01	00	15	15	30	05	01	20	10	02	02	70	02	02	10	10	02
Y27	.068	90	10	00	20	60	05	10	05	60	70	20	01	05	10	05	02	50	02	02	03	10	02
Y28	.001	30	30	30	05	01	05	10	01	10	20	01	01	01	01	05	02	70	02	02	05	30	02
Y29	.001	60	38	01	01	01	01	80	30	10	50	05	20	01	20	05	02	50	02	02	10	30	02
Y30	.252	15	70	15	01	01	01	00	01	20	30	05	01	15	05	05	20	95	05	02	10	10	05
Y31	.081	30	60	10	30	50	10	00	05	60	70	20	10	20	10	05	01	50	10	02	05	05	25
Y32	.005	30	40	30	01	01	05	50	01	20	30	10	01	10	05	02	02	10	10	02	02	20	10
Y33	.040	10	55	05	50	20	10	00	01	80	90	20	01	30	05	05	10	70	05	02	10	30	10

	X23	X24	X25	X26	X27	X28	X29	X30	X31	X32	X33	X34	X35	X36	X37	X38	X39	X40	X41	X42	X43	X44	X45	X46	X47	X48	X49	X50
	05	01	00	01	01	15	05	10	03	01	01	01	02	02	02	02	02	01	00	02	70	04	03	00	00	80	05	10
	02	01	01	01	01	60	01	80	01	01	01	70	05	05	85	02	02	01	02	01	30	02	20	05	01	90	01	60
	03	01	01	01	02	30	15	40	01	05	01	85	05	20	70	02	02	01	01	01	05	01	05	60	01	38	01	70
	01	01	01	01	01	95	01	50	01	05	01	85	05	20	70	02	02	01	02	01	15	20	02	05	01	10	01	40
	01	01	01	01	01	70	02	40	10	10	01	65	70	05	85	02	02	15	01	85	05	02	20	02	20	20	20	80
	05	01	01	10	15	40	02	10	01	01	01	15	02	02	15	02	02	02	02	02	20	02	02	02	02	60	02	30
	20	01	01	10	15	85	02	80	01	01	01	90	02	25	75	02	02	02	02	30	10	01	30	05	01	80	02	70
	05	01	01	01	01	02	60	01	20	30	01	02	90	02	02	90	10	05	02	50	15	05	02	20	20	20	20	50
	05	01	01	01	01	02	35	10	20	10	01	10	02	02	60	02	02	25	25	45	45	25	15	15	05	05	50
	05	02	02	10	15	10	60	20	01	02	01	95	02	85	10	02	02	02	02	20	05	02	02	60	05	25	05	90
	05	02	02	10	15	10	60	20	01	02	01	95	02	85	10	02	02	02	02	20	05	02	02	60	05	25	05	90
	10	02	02	01	01	10	60	20	01	05	01	95	02	85	10	02	02	01	01	01	10	02	02	68	01	25	01	80
	02	02	02	01	01	10	60	20	01	05	01	95	02	85	10	02	02	01	01	01	10	01	01	68	01	25	01	80
	05	02	02	10	10	01	90	20	01	02	01	95	02	85	10	02	02	02	01	30	40	02	05	01	01	02	02	20
	01	20	02	50	05	10	02	10	01	01	01	10	02	10	02	02	02	01	01	02	02	01	60	02	01	25	02	60
	02	02	02	02	02	95	00	30	01	10	91	95	02	90	05	02	02	01	01	01	30	15	05	02	02	05	02	20
	20	02	02	02	02	70	01	40	01	01	01	01	15	02	02	02	05	19	02	10	20	05	02	02	02	10	05	75
	85	02	02	03	05	50	01	20	40	02	01	02	10	02	02	50	05	10	02	05	10	02	02	05	02	20	10	85
	05	01	01	05	70	05	05	20	01	01	01	05	05	02	02	02	02	02	02	10	10	02	02	05	02	10	10	30
	02	02	02	01	01	50	01	20	05	02	01	50	02	10	40	02	02	20	20	10	10	10	05	05	10	10	70
	02	10	02	01	01	20	02	10	50	02	01	05	10	05	05	40	90	02	02	10	10	02	02	02	05	05	10
	01	01	01	01	01	46	02	01	05	01	01	05	10	05	05	20	90	01	01	01	01	01	01	01	01	01	10
	01	95	05	01	01	20	10	01	40	01	05	05	15	02	02	70	15	02	02	02	20	10	02	05	01	05	01	90
	01	95	05	01	01	20	10	01	40	01	05	05	15	02	02	70	15	02	02	02	20	10	02	05	01	05	01	90
	05	15	10	80	15	10	10	01	30	01	99	05	05	02	02	40	04	01	01	05	20	10	02	02	02	10	05	05
	02	02	02	05	10	40	10	30	05	01	01	30	10	40	10	20	05	02	02	40	40	02	02	10	10	10	10	40
	02	05	02	01	01	20	10	20	20	02	02	40	20	30	05	20	05	02	02	30	30	02	02	03	03	10	10	50
	02	05	02	01	01	20	10	10	10	01	01	20	10	10	10	10	10	02	02	30	30	02	02	05	05	30	30	60
	02	05	02	01	01	90	02	40	05	01	10	70	05	80	05	10	05	02	02	30	30	02	02	10	10	30	30	20
	01	02	05	01	01	30	02	05	30	01	01	30	10	05	05	15	05	20	02	92	05	05	01	01	10	01	05	85
	01	02	05	01	01	90	02	30	05	05	01	50	05	75	15	10	05	01	01	30	30	10	02	01	05	01	05	50
	02	02	02	02	02	90	02	30	05	05	01	70	05	75	15	10	05	02	02	10	10	02	02	02	02	20	20	20
	02	02	01	01	01	30	10	01	20	30	01	02	90	02	02	90	10	10	02	30	30	05	05	10	10	30	30	50

FIGURE 11

Symptom-disease matrix for a Bayesian congenital heart disease diagnostic model.

studies and observation at surgery at least as often as does the most probable diagnosis estimated by three experienced cardiologists from the same clinical information. Furthermore, the differential diagnosis resulting from solution of the equation is frequently more complete, and, in retrospect, often appears more logical to clinicians than the differential diagnosis listed by each of them prior to seeing the equation's prediction." [44]

"For most radiologists, having a patient with a primary bone tumor can be considered a rare event, and it is difficult for a radiologist to accumulate in a lifetime a significant experience in the radiological diagnosis of bone tumors."[45] The work of Lodwick[46,47] suggests that a Bayesian model can be of great assistance to a radiologist confronted with films suggestive of a bone tumor. To be of value to the clinician, two criteria must be met. The system must be organized so that the clinician is not overwhelmed by the complexity of computer language. Second, definitions must be provided for any symptoms or terms on which a universal opinion does not exist or subjective influence can occur.

Lodwick has presented his Bayesian model in the form of a brochure containing several forms (Figures 12 and 13) which explain the system. Data is entered onto punch cards and a Bayesian analysis performed using Lodwick's

Relative to long axis

central   eccentric   cortex and/or parosteal

Relative to pelvis   Relative to long bones
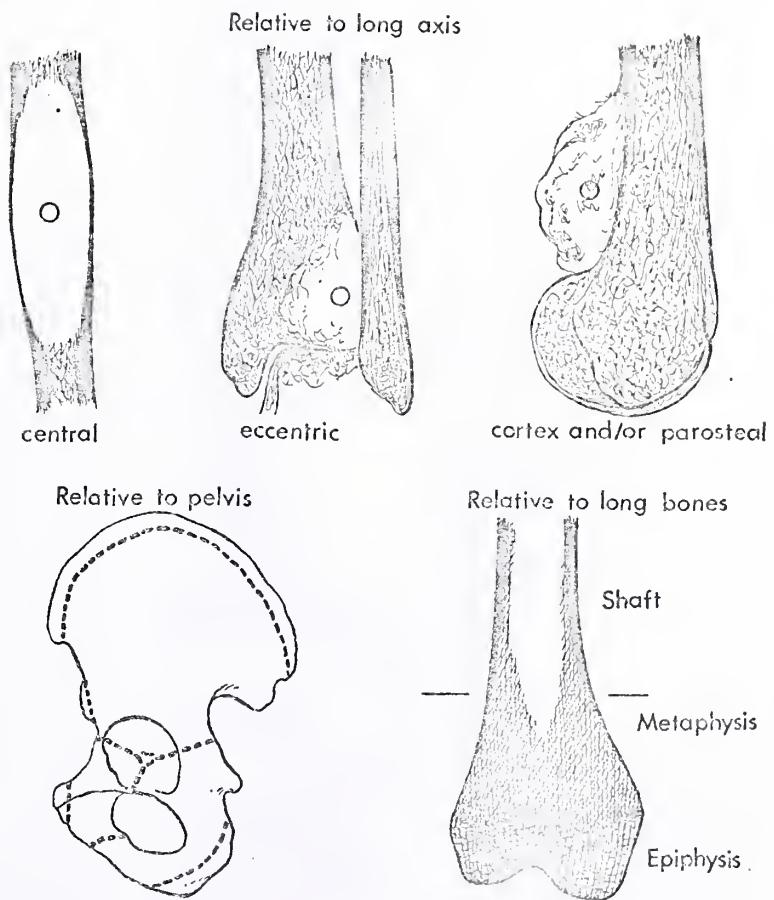
Shaft

Metaphysis

Epiphysis

FIGURE 12

FIGURE 12

Guidelines for a Bayesian bone tumor diagnostic model.

From: Lusted, Lee, Introduction to Medical Decision Making
(Springfield, Illinois, Charles Thomas, 1968).

TABLE 1. FORM USED IN COMPUTER-AIDED GRADING AND DIAGNOSIS OF PRIMARY BONE TUMORS
(Delay in diagnosis and 5-year survival are not used by the computer)

Case Number (1–6) ....

1. Clinical data		Col.	Yes	No
Sex	Male	7	1	0
Age	0–9	8	1	2
	10–19	9	1	2
	20–29	10	1	2
	30–39	11	1	2
	≥ 40	12	1	2

Months delay
in diagnosis

	Col.	Yes	No
0	13	1	2
1–2	14	1	2
3–11	15	1	2
≥ 12	16	1	2

Five years survival
from diagnosis

	Col.	Yes	No
	17	1	0

2. Size	mm	Col.	Yes	No
	00	18	1	2
	01–30	19	1	2
	31–60	20	1	2
	61–90	21	1	2
	91 up	22	1	2

3. Location	Col.	Yes	No
Central	23	1	2
Eccentric	24	1	2
Cortex or surface	25	1	2
Pelvis or sacrum	26	1	2
Other flat bones, including ribs, skull, mandible	27	1	2
Small bones, including patella	28	1	2
Tubular bones, including clavicles	29	1	2

Subdivisions of
tubular bones

	Col.	Yes	No
Articular surface	30	1	0
Epiphysis	31	1	0
Growth plate	32	1	0
Metaphysis	33	1	0
Shaft	34	1	0

4. Tumor matrix mineralization	Col.	Yes	No
Radiolucent	35	1	0
Cloudy	36	1	0
Flocculent	37	1	0
Lumpy	38	1	0
Solid	39	1	0

5. Destruction of bone	Col.	Yes	No
Geographic	40	1	0
Moth-eaten	41	1	0
Permeated	42	1	0
Fracture	43	1	0
Displacement	44	1	0
Regular margin	45	1	0
Lobulated margin	46	1	0
Ragged margin	47	1	0
Indistinct margin	48	1	0
Sharp edge	49	1	0
Smudged edge	50	1	0
Invasive edge 1 cm	51	1	0
Inv. edge gr. 1 cm	52	1	0

Penetration of cortex

	Col.	Yes	No
None	53	1	2
Partial	54	1	2
Total	55	1	2

6. Proliferation of bone	Col.	Yes	No
Sclerotic rim	56	1	0
Mottled	57	1	0
Endostotic	58	1	0
Hyperostotic	59	1	0
Trabeculated	60	1	0
Buttressed	61	1	0
No expanded cortex	62	1	2
Expanded 10 mm	63	1	2
Expanded 11 mm up	64	1	2
No Codman's triangle	65	1	2
1 Codman's	66	1	2
2 Codman's	67	1	2
3 or more Codman's	68	1	2
No periostosis	69	1	2
Laminated perio.	70	1	2
Amorphous perio.	71	1	2
No spiculation	72	1	2
Regular	72	1	2
Hair-on-end	74	1	2
Velvet	75	1	2

NOTE: Within each bracketed group only *one* item may be checked *yes*.

FIGURE 13

Questionnaire for a Bayesian bone tumor diagnostic model.

From: Lodwick, Gwilym, et al., "Computer Aided Diagnosis of Radiographic Images" Journal of Chronic Diseases (Volume 19, No. 4, April, 1966) p. 489.

"prior distribution" tables. The accuracy of the
system is high, with greater than ninety percent agree-
ment with the histological type for nine cell categories.
The data analysis was tested using two separate matrices,
the first based on data from a Sarcoma Registry, the
literature and Lodwick's personal file; the second,
employing greater input from Lodwick's personal exper-
ience and expectations. Interestingly, the second
symptom-disease matrix yielded results five percent
better than the first.

A criticism often levelled at computer-dependent
diagnostic models is their relative inaccessibility;
the results frequently are not available until after
the clinical diagnosis has been obtained. The largest
Bayesian study to date, a model for the diagnosis of
abdominal pain,[48,49] offers a solution. The study involves
an "on-line" facility within the Professorial Surgical
Unit at Leeds, England, into which the clinician "logs"
the appropriate information. Following the Bayesian
computations, the teletypewriter prints a "hardcopy"
including a summary of the diagnostic findings, the
computer's "diagnoses", a list of additional physical
findings to reexamine, and finally, a listing of rarer
diseases to be included in the differential diagnosis
but too rare to provide a sufficient data base for computer
analysis.

The symptoms used in the model (Figure 14) are the standard ones employed in the diagnosis of the "acute abdomen". Seven diagnoses - acute appendicitis, diverticular disease, perforated peptic ulcer, acute cholecystitis, acute intestinal obstruction, acute pancreatitis and non-specific abdominal pain - were chosen for the study since they represented over ninety-five percent of all admissions to this unit with acute abdominal pain. The entity, non-specific abdominal pain, while not an accepted medical entity,[50] played a significant role in the study. DeDombal[51] has noted that every experienced surgeon encounters a significant number of patients with acute abdominal pain who fit none of the other disease patterns. In some, the pain subsides spontaneously and the patient is sent home undiagnosed, others come to "negative laparotomy", a third group have a medical problem not requiring surgical approach, for example, a urinary tract infection, and still others have psychophysiologic pain. Thus, it is important to have a category for those patients admitted to a surgical unit with acute abdominal pain for whom no surgical diagnosis can be obtained and surgical intervention is inappropriate.

To qualify for the study, the criteria were:

    1. patient presented with a chief complaint of abdominal pain

FIG. 3—Example of case history, showing form on to which patient data are copied for later entry into the computer.

FIGURE 14

Questionnaire for a Bayesian abdominal pain diagnostic model.

From: Horrocks, J.C., et al., "Computer-Aided Diagnosis" British Medical Journal (Volume 2, April 1, 1972) p. 6.

2. the pain was of less than one week's
   duration

3. the admission was an emergency procedure
   through the emergency room

4. the patient had not previously entered
   into the study

5. the patient was capable of giving a history
   (this excluded only two patients, a
   baby aged two weeks and a comatose
   patient)

6. a diagnosis was eventually made (excluding
   one patient for whom a histological
   diagnosis was indecisive).

The results of the study are striking. Compared to
each clinician, the computer yielded consistently better
results, as shown in Figure 15. The diagnosis of acute
appendicitis, the most frequent cause of the acute
abdomen, provided data of great interest. Of the eighty-
five patients with acute appendicitis, the computer
diagnosed 84. The Senior clinicians recognized only 75
and classified six into the non-operative category, often
delaying surgery several hours. While the computer erred
in diagnosing nine additional patients as having acute
appendicitis, the clinicians (without knowledge of the
computer's diagnosis) performed more than twenty negative
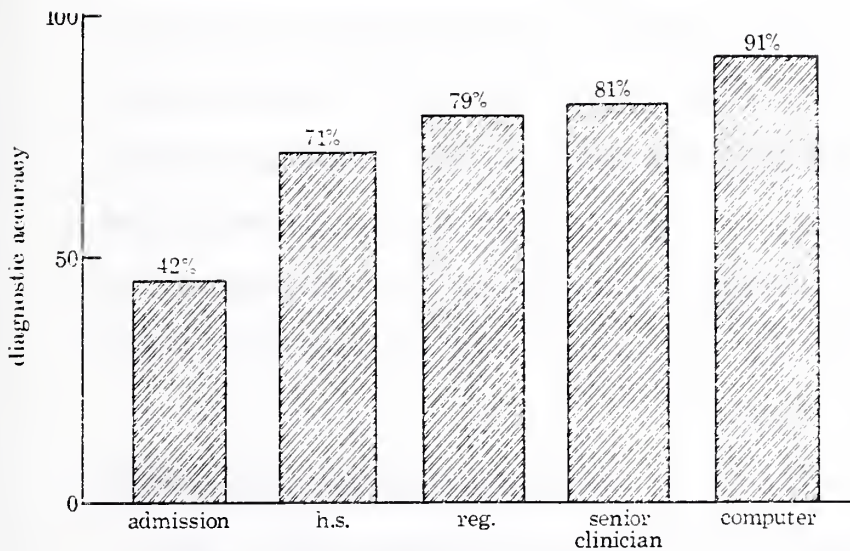
FIGURE 2. Comparison of overall human and computer-aided diagnostic accuracy.

FIGURE 15

From: deDombal, F.T., "Surgical Diagnosis assisted by a Computer" Proceedings of the Royal Society of London (Volume 184, 1973) p. 437.

laparotomies, including those nine. DeDombal states, "We cannot resist pointing out two facts. First, the cost of performing a 'negative laparotomy' and keeping the patient in the hospital for a week postoperatively is rarely less than Ƀ200 ($500); and the system would have obviated the need for 34 such operations [in a larger series]. More important perhaps, diagnostic delay which results in perforation of an appendix increases the mortality of appendectomy tenfold; the system's predictions would have helped to minimize such delay."[52]

Other diagnostic models

Two other diagnostic models are worthy of comment although it is difficult to classify them into the previous categories. In a monograph entitled "Diagnostic Computers", Caceres and Rikli[53] describe an operational computer program to "read" electrocardiograms and propose diagnoses. The protocol involves:

1. minimization of "noise" from the circuitry
2. choosing a fiducial point
3. determination of significant reference points
4. pattern recognition routines.

Once the wave patterns are recognized, the data is "condenced to those values significant to diagnosis by

a discriminant function analysis,"[54] and tested through multiple combinations. For example, "the diagnosis of 'acute diaphragmatic myocardial infarction' is pursued by checking for the presence of a pre-determined positive value for Q duration, for negative T waves, and for elevated ST segments".[55] To obtain the final EKG diagnosis, "All of the resultant diagnostic statements are initally considered as only tentative. Those which are redundant or secondary to diagnosis of greater strength are discarded".[56]

To compare the program to a clinician, 750 routine EKGs, of which approximately twenty-five percent were normal, were presented to an independent cardiologist (one not aware of the criteria employed by the program) and to the computer. There was complete agreement in about 73% of the readings. In 26%, clinician and computer agreed that the tracing was abnormal, but disagreed on the nature of the abnormality. In 0.8 percent of the cardiograms, the computer read as normal something considered abnormal by the clinician. The vast majority of these were felt to be "analog magnetic tape playback, digitilization and artifacts".[57]

The authors foresaw improvement in diagnostic accuracy with technical refinements and additional arrhythmia routines. Considering the estimated cost of between two and four dollars per reading, with improvements the program

could be viable for clinical use.

Diagnostic Criteria

The diagnosis of certain medical diseases, particularly
collagen disorders, is difficult because of the variety
of presentations of the same disease. To surmount this
problem, it has been necessary to establish diagnostic
criteria. At the meetings of the American Rheumatism
Association in 1954, there was a demand for precise
diagnostic criteria for rheumatoid arthritis.   In 1956,
a committee headed by Ropes[58] proposed criteria for the
classes of "definite, probable and possible rheumatoid
arthritis." After two years of use, the lack of rigor
in the criteria was criticized and revised criteria[59]
were published, adding a fourth category, classical
rheumatoid arthritis.

The criteria (Figure 16), while controversial, were
felt to have a number of benefits. Most importantly,
medical school faculty "have found these criteria helpful
as a framework from which to discuss the disease. This
has proved true even for some ... who disagree with the
criteria or some portion thereof, for they still have a
framework from which to operate and a specific opportunity
can then be made to express differing points of view."[60]

Classical Rheumatoid Arthritis

This diagnosis requires seven of the following criteria. In criteria 1 through 5, the joint signs or symptoms must be continuous for at least six weeks. (Any one of the features listed under Exclusions will exclude a patient from this category.)

1. Morning stiffness.
2. Pain on motion, or tenderness in at least one joint (observed by a physician).
3. Swelling (soft tissue thickening or fluid—not bony overgrowth alone) in at least one joint (observed by a physician).
4. Swelling (observed by a physician) of at least one other joint (any interval free of joint symptoms between the two joint involvements may not be more than 3 months).
5. Symmetric joint swelling (observed by a physician) with simultaneous involvement of the same joint on both sides of the body (bilateral involvement of midphalangeal, metacarpophalangeal, or metatarsophalangeal joints is acceptable with absolute symmetry). Terminal phalangeal joint involvement will not satisfy this criterion.
6. Subcutaneous nodules (observed by a physician) over bony prominences, on extensor surfaces, or in juxta-articular regions.
7. X-ray changes typical of rheumatoid arthritis (which must include at least bony decalcification localized to or greatest about the involved joints and not just degenerative changes). Degenerative changes do not exclude patients from any group classified as rheumatoid arthritis.
8. Positive agglutination test—demonstration of the "rheumatoid factor" by any method that, in two laboratories, has been positive in not over 5 percent of normal controls—or positive streptococcal agglutination test.
9. Poor mucin precipitate from synovial fluid (with shreds and cloudy solution).
10. Characteristic histologic changes in synovial membrane with three or more of the following: marked villous hypertrophy; proliferation of superficial synovial cells, often with palisading; marked infiltration of chronic inflammatory cells (lymphocytes or plasma cells predominating) with tendency to form "lymphoid nodules;" deposition of compact fibrin, either on surface or interstitially; foci of cell necrosis.
11. Characteristic histologic changes in nodules showing granulomatous foci with central zones of cell necrosis, surrounded by proliferated fixed cells, and peripheral fibrosis and chronic inflammatory cell infiltration, predominantly perivascular.

Definite Rheumatoid Arthritis

This diagnosis requires five of the foregoing criteria. In criteria 1 through 5, the joint signs or symptoms must be continuous for at least six weeks. (Any one of the features listed under Exclusions will exclude a patient from this category.)

Probable Rheumatoid Arthritis

This diagnosis requires three of the above criteria. In at least one of the criteria, 1 through 5, the joint signs or symptoms must be continuous for at least six weeks. (Any one of the features listed under Exclusions will exclude a patient from this category.)

Possible Rheumatoid Arthritis

This diagnosis requires two of the following criteria, and the total duration of joint symptoms must be at least three weeks. (Any one of the features listed under Exclusions will exclude a patient from this category.)

1. Morning stiffness.
2. Tenderness or pain on motion (observed by a physician) with history of recurrence or persistence for three weeks.
3. History or observation of joint swelling.
4. Subcutaneous nodules (observed by a physician).
5. Elevated sedimentation rate or C-reactive protein.
6. Iritis

Exclusions

1. The typical rash of _disseminated lupus erythematosus_ (with butterfly distribution, follicle plugging, and areas of atrophy).
2. High concentration of _lupus erythematosus_ cells (4 or more in 2 smears prepared from heparinized blood incubated not over 2 hrs.).
3. Histologic evidence of _periarteritis nodosa_ with segmental necrosis of arteries associated with nodular leukocytic infiltration extending perivascularly and tending to include many eosinophils.
4. Weakness of neck, trunk, and pharyngeal muscles or persistent muscle swelling of _dermatomyositis_.
5. Definite _scleroderma_ (not limited to the fingers).
6. A clinical picture characteristic of _rheumatic fever_ with migratory joint involvement and evidence of endocarditis, especially if accompanied by subcutaneous nodules, erythema marginatum, or chorea. (An elevated antistreptolysin titer will not rule out the diagnosis of rheumatoid arthritis.)
7. A clinical picture characteristic of _gouty arthritis_ with acute attacks of swelling, redness, and pain in one or more joints, especially if relieved by colchicine.
8. _Tophi._
9. A clinical picture characteristic of acute _infectious arthritis_ of bacterial or viral origin with an acute focus of infection, or in close association with a disease of known infectious origin; chills; fever; and an acute joint involvement, usually migratory initially (especially if there are organisms in the joint fluid or if there is response to antibiotic therapy).
10. _Tubercle bacilli_ in joints or histologic evidence of joint tuberculosis.
11. A clinical picture characteristic of _Reiter's syndrome_ with urethritis and conjunctivitis associated with acute joint involvement, usually migratory initially.
12. A clinical picture characteristic of the _shoulder-hand syndrome:_ unilateral involvement of shoulder and hand with diffuse swelling of the hand followed by atrophy and contractures.
13. A clinical picture characteristic of _hypertrophic pulmonary osteoarthropathy_ with clubbing of fingers and/or hypertrophic periositis along the shafts of the long bones, especially if an intrapulmonary lesion is present.
14. A clinical picture characteristic of _neuroarthropathy_ with condensation and destruction of bones of involved joints and with associated neurologic findings.
15. _Homogentisic acid_ in the urine, detectable grossly with alkalinization.
16. Histologic evidence of _sarcoid_ or positive Kveim test.
17. _Multiple myeloma_ as evidenced by marked increase in plasma cells in the bone marrow, or Bence Jones protein in the urine.
18. Characteristic skin lesions of _erythema nodosum._
19. _Leukemia or lymphoma_ with characteristic cells in peripheral blood, bone marrow, or tissues.
20. _Agammaglobulinemia._

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CHAPTER   III

Bayes Theorem

It was in 1763 that Bayes[1] first proposed his theorem
of prior distributions. Despite numerous onslaughts
from the world of mathematics, it has appeared repeatedly
in scientific literature and has recently entered the
medical literature, dealing with problems of diagnosis
or prognosis.

Prior to defining the theorem, it is necessary to
define a number of mathematical terms. These appear
in Figure 17.

In mathematical theory, the probability of an event
is a number between zero (an impossible event) and one
(a certainty). Typically, the result lies between and
can be defined as:

$$P(D) \quad = \quad N(D)/N,$$

the ratio of the number of people with the disease to
the entire population. Similarly, the probability of a
symptom can be defined as:

$$P(S) \quad = \quad N(S)/N.$$

FIGURE 17

N	Number of people in the population
N(D)	Number of people in this population with disease D
N(S)	Number of people with symptom S
N(D $\cap$ S) or N(S $\cap$ D)	Number of people with both the disease D and the symptom S
P(D)	Probability of disease D
P(S)	Probability of symptom S
P(S $\cap$ D) or P(D $\cap$ S)	Probability of both the disease D and the symptom S
$P(S_1, S_2, \ldots S_n)$	Probability of a set of symptoms $S_1, S_2, \ldots, S_n$
P(D/S)	Probability of disease D, given symptom S
P(S/D)	Probability of symptom S, given disease D
$P(D/S_1, S_2, \ldots, S_n)$	Probability of disease D, given a set of symptoms, $S_1, S_2, \ldots, S_n$

Figure 17

N	Number of people in the population
$N(D)$	Number of people in the population with disease D
$N(S)$	Number of people with symptom S
$N(D \cap S)$ or $N(S \cap D)$	Number of people with both the disease D and the symptom S
$P(D)$	Probability of disease D
$P(S)$	Probability of symptom S
$P(S \cap D)$ or $P(D \cap S)$	Probability of both the disease D and the symptom S
$P(S_1,S_2,...,S_n)$	Probability of a set of symptoms $S_1,S_2,...,S_n$
$P(D/S)$	Probability of disease D, given symptom S
$P(S/D)$	Probability of symptom S, given disease D
$P(D/S_1,S_2,...,S_n)$	Probability of disease D, given a set of symptoms, $S_1,S_2,...,S_n$

The probability of a symptom being present, given a disease, is proportional to the number of patients having both the symptom and the disease, and inversely to the number of patients having the disease, that is:

$$P(S/D) = N(S \cap D)/N(D).$$

In the special case $N(D) = 0$, the formula is invalid and $P(S/D)$ is undefined. Dividing both numerator and denominator by N yields:

$$P(S/D) = \frac{N(S \cap D)/N}{N(D)/N}$$

This can be simplified to:

$$P(S/D) = P(S \cap D)/P(D) \tag{1}$$

A similar derivation yields the result:

$$P(D/S) = P(S \cap D)/P(S)$$

Crossmultiplying yields:

$$P(S \cap D) = P(D) \cdot P(S/D)$$

$$P(S \cap D) = P(S) \cdot (P(D/S)$$

Thus:

$$P(D) \times P(S/D) = P(S) \times P(D/S)$$

In a different form (excluding the case in which $P(S) = 0$:

$$P(D/S) = \frac{P(D) \cdot P(S/D)}{P(S)}$$

This is Bayes Law. It states that the probability of a disease being present is proportional to three factors: directly to the incidence of the disease as well as the probability of the symptoms within the disease, and inversely to the probability of the symptoms with the population. It is important to note that no assumptions have been made regarding the nature of the distributions and the inter- or independence of symptoms or diseases. Other than the assumption that the denominator cannot be zero, it has been demonstrated that the probability of a disease being present given a set of symptoms can be universally defined by three pieces of data - the probability of a symptom within a disease and the probability of each the symptom and disease within the population being studied (a community, country or clinic population, for example). An example offered by Mount and Evans [2] can illustrate the use of Bayes Law. A population of one thousand persons is distributed with regard to a symptom and disease as follows:

1. 100 patients have both the disease and symptom

2. 200 patients have the disease but not the symptom

3. 300 patients have neither the disease nor the symptom

     4.   400 patients do not have the disease but

have the symptom.

These statements are equivalent to:

     1. $N(S \cap D) = 100$

     2. $N(\bar{S} \cap D) = 200$

     3. $N(\bar{S} \cap \bar{D}) = 300$

     4. $N(S \cap \bar{D}) = 400$

in which $\bar{S}$ and $\bar{D}$ imply respectively, those without the symptom and those without the disease. It is simple to compute:

$$P(D) = P(D \cap S) + P(D \cap \bar{S})$$
$$= 100/1000 + 200/1000$$
$$= 0.3$$

and,

$$P(S) = 100/1000 + 400/1000$$
$$= 0.5$$

Using Equation (1):

$$P(S/D) = P(S \cap D)/P(D)$$
$$= 0.1/0.3$$
$$= 0.33$$

To determine the probability of a patient having this disease, with the knowledge that the patient has the symptom, one can use Bayes Law:

$$P(D/S) = P(D)P(S/D)/P(S)$$

$$= 0.3 \times 0.33/0.g$$

$$= 0.2.$$

This value could be derived by direct examination of the data with complete agreement.

Diseases are not typically represented by one symptom but more likely by a set of symptoms, physical findings or laboratory abnormalities. Symptoms are better seen as complexes. Instead of $P(S)$, it is more appropriate to employ the term $P(S_1, S_2, \ldots, S_n)$ and Bayes Law becomes:

$$P(D/S_1, S_2, \ldots, S_n) = \frac{P(D) \cdot P(S_1, S_2, \ldots, S_n/D)}{P(S_1, S_2, \ldots, S_n)}$$

In addition, the absence of a symptom is as important to consider as its presence. The probabilty of $\overline{S}_j$ - the symptom S_j being absent - is equal to $1-P(S_j)$.

In the simplest of clinical situations, one is concerned with the presence or absence of a single disease. This is equivalent to $P(D) + P(\overline{D}) = 1$, that is , the patient either has, or does not have the disease; no other possibilities are tenable. If two or more diseases are considered, the patient must always have some disease or be normal:

$$P(D_1) + P(D_2) + \ldots + P(D_n) + P(\text{normal}) = 1.$$

For the sake of simplification, the state normal is either included as an additional disease state or ignored.

The terms P(S) can also be expanded, to:

$$P(S) = P(S/D_1)P(D_1) + P(S/D_2)P(D_2) + \ldots + P(S/D_m)P(D_m)$$

Combining these, Bayes Law becomes:

$$P(D_i/S_1,\bar{S}_2,\ldots,S_n) = \frac{P(S_1,\bar{S}_2,\ldots,S_n/D_i)P(D_i)}{P(S_1,\bar{S}_2,\ldots,S_n/D_1)P(D_1) +}$$

$$P(S_1,\bar{S}_2,\ldots,S_n/D_2)P(D_2) + \ldots +$$

$$P(S_1,\bar{S}_2,\ldots,S_n/D_i)P(D_i) + \ldots +$$

$$P(S_1,\bar{S}_2,\ldots,S_n/D_m)P(D_m)$$

still without having made any assumptions.

To apply Bayes Law to clinical situations, it is necessary to know only the following information:

1. the incidence (or prevalence, if appropriate) of the disease within the population being studied, and,

2. the probability of the symptom complex being present within each of the diseases under consideration.

The first is accessible through the medical literature or public health data. If the population under consideration is a clinic group, the data can be predicted from personal experience. The second is somewhat more complex. Medical literature generally contains information in the form of P(S/D) for each individual symptom. Only rarely does the literature propose to give $P(S_1, S_2/D)$, the occurence

of two symptom complexes within a disease. Even rarer

does it propose to deal with more extensive symptom

complexes for any disease.

To obtain sufficient data would require a review

of a large number of cases, proportional to m x 2^n for

m disease and n symptoms, each having only two possible

states, present or absent. As the number of symptoms

becomes large or the states for any one symptom increases

(for example, a symptom graded as absent, mild, moderate

or severe) the task becomes untenable: the required

sample would quickly exceed all human population, past

or present.

To simplify this task, this study, as well as all

the Bayesian studies in the literature, assumes the

independent sorting of symptoms within each disease. If

independent, the incidence of a set of symptoms can be

expanded to:

$$P(S_1, S_2, \ldots, S_n) = P(S_1)P(S_2)\ldots P(S_n)$$

and Bayes Law becomes:

$$P(D_i/S_1, S_2, \ldots, S_n) = \frac{P(D_i)P(S_1/D_i)P(S_2/D_i)\ldots P(S_n/D_i)}{\begin{array}{l} P(D_1)P(S_1/D_1)P(S_2/D_1)\ldots P(S_n/D_1) \; + \\ P(D_2)P(S_1/D_2)P(S_2/D_2)\ldots P(S_n/D_2) + \ldots + \\ P(D_m)P(S_1/D_m)P(S_2 D_m)\ldots P(S_n/D_m) \end{array}}$$

Theoretically, this cannot be true, as demonstrated by

Lusted. "Two symptoms S_1 and S_2 relevant to a disease D

cannot be independent of each other unconditionally since the truth or falsehood about the hypothesis of what disease causes S_1 and S_2 will cause the symptoms, if they are indeed diagnostically relevant, to co-vary."[3] Warner[4] dealt with this problem through the mathematical demonstration that for a symptom to be truly independent of another woud require a uniform distribution through the population. Consequently, the symptom would be of no diagnostic value. The use of non-independent symptoms is valid if the correlation "is due only to the non-uniform distribution of x_b in diseases $y_1, y_2, \ldots, y_k$ and not due to a direct causal relationship between x_a and x_b."[5]

Lodwick states "Our version of Bayes rule assumes that our predictor findings are independent, which is to say that information regarding the presence or absence of one finding does not provide information regarding the probability of the presence or absence of any other findings. One can at best only demonstrate correlation between findings in a given sample. The absence of correlation merely suggests the possibility of independence; it can by no means be accepted as proof. Thus, we would appear to be on theoretically shaky grounds to use Bayes theorem in the form we use it."[6]

In practice, independence of symptoms can be
tested through chi-squared analysis. If present, highly
correlated symptoms can be combined; symptoms, which
are causally related, can be eliminated. For example,
it would be in error in a congenital heart disease
model to employ both cyanosis and pO_2 levels; their
correlation, while dependent on other factors, is too
high to allow their simultaneous use.

Alternatively, a complicated mathematical procedure
can be employed. Brunk and Lehr,[7] using the Gram
Schmidt Orthoginalization Procedure, discard symptoms
with a high correlation. Those with weaker correlations
selected individually and a linear function of one variable
is subtracted from another so that they are no longer
correlated. Then another variable is selected, the same
function performed, until a set of uncorrelated variables
is obtained.

Despite this limitation, Lusted warns against ignoring
Bayes Law. "How seriously should you take your inability
to prove that symptoms are independent? One answer is
that you should not take it seriously enough to discourage
you from using Bayesian procedures to study medical diag-
nosis. You can assume that symptoms are conditionally
independent even when you have reason to suppose they
are not. ..., but you should not take the situation too
glibly. Watch for violations of conditional independence

which are so severe that they may lead you to major errors in diagnosis ...."[8]

To illustrate the use of Bayes Law, a symptom disease matrix is shown below.

	Incidence	$P(S_1)$	$P(S_2)$	$P(S_3)$
D	0.25	.2	.3	.9
$\overline{D}$	0.75	.7	.4	.4

A patient under consideration has symptoms S_1 and S_3 but not S_2. Using Bayes Law:

$$P(D/D_1,\overline{S}_2,S_3) = \frac{P(D)P(S_1,\overline{S}_2,S_3/D)}{P(D)P(S_1,\overline{S}_2,S_3/D) + P(\overline{D})P(S_1,\overline{S}_2,S_3/D)}$$

$$= \frac{P(D)P(S_1/D)P(\overline{S}_2/D)P(S_3/D)}{P(D)P(S_1/D)P(\overline{S}_2/D)P(S_3/D) + P(\overline{D})P(S_1/\overline{D})P(\overline{S}_2/\overline{D})P(S_3/\overline{D})}$$

Remembering that $P(\overline{S})$ is equal to $1 - P(S)$:

$$P(D/S_1,\overline{S}_2,S_3) = \frac{(.25)(.2)(1-.3)(.9)}{(.25)(.2)(1-.3)(.9) + (.75)(.7)(1-.4)(.4)}$$

$$= 0.2$$

Similarly,

$$P(\overline{D}/S_1,\overline{S}_2,S_3) = \frac{P(\overline{D})P(S_1,\overline{S}_2,S_3/\overline{D})}{P(\overline{D})P(S_1,\overline{S}_2,S_3/\overline{D}) + P(D)P(S_1,\overline{S}_2,S_3/D)}$$

$$= \frac{(.75)(.7)(1-.4)(.4)}{(.75)(.7)(1-.4)(.4) + (.25)(.2)(1-.3)(.9)}$$

$$= 0.8$$

Thus, the probability of the disease, given these symptoms, is 0.2 (twenty percent) and the probability of the disease not being present is 0.8 (eighty percent).

One final comment on Bayes Law relates to the simultaneous occurrence of two diseases. The data in the symptom-disease matrix relates only to each individual disease. Bayes Law does not permit assumptions regarding the simultaneous occurrence of two diseases: this case must be handled as a new disease pattern. Neither a ventricular septal defect nor pulmonary stenosis alone can cause cyanosis, yet in combination they are likely to do so. A Bayesian model employing the two diseases separately is incapable of diagnosing the combined condition: to diagnosis a VSD with pulmonary stenosis would require data on this third disease.

In the following chapters, a model employing Bayes Law for the diagnosis of neonatal heart disease will be described. In considering the model and its use of Bayes Law, it is important to remember that independence of variables was assumed to allow one to expand Bayes Law to its final form. Beyond this, Bayes Law is of universal validity: it allows its user to predict the likelihood of a disease from a set of symptoms. The only information required for this prediction is the incidence of each disease under consideration and the probability of each symptom within each disease.

FOOTNOTES

1.   T. Bayes, "Essay towards solving a problem in the
      doctrine of chances" _Philosophical Transactions
      of the Royal Society_ (Volume 53, 1763) pp. 370-
      418 (Reprinted in _Biometrika_ (Volume 45, 1958)
      pp. 293-315).

2.   James Mount, John Evans, "Computer-Aided Diagnosis-
      A Simulation Study" _Proceedings of the Fifth
      IBM Medical Symposium_ (1963) pp. 113-127.

3.   Lee Lusted, _Introduction to Medical Decision Making_
      (Charles Thomas, Springfield, Illinois, 1968).

4.   Homer Warner, Alan Toronto, George Veasy, Robert
      Stephenson, "A Mathematical Approach to Medical
      Diagnosis" _Journal of the American Medical Associa-
      tion_ (July 22, 1961, Volume 177, No. 3) p. 178.

5.   _Ibid._, p. 179.

6.   Gwilym Lodwick, "Computer-Aided Diagnosis in Radiology.
      A Research Plan" _Investigative Radiology_ (January,
      February, 1966, Vol. 1) pp. 75-76.

7.   H. D. Brunk, J. L. Lehr, "An Improved Bayes Method for
      Computer Diagnosis" _Proceedings of Conference on
      the Use of Computers in Radiology_ (University of
      Chicago, Center for Continuing Education, October 22,
      1966).

8.   Lusted, _Op. Cit._, p. 18.

CHAPTER IV

METHODOLOGY

With the development of high-speed electronic computers, it became practical to apply Bayes Law to the solution of complex clinical problems. As mentioned previously, models have been developed for the diagnosis of congenital heart disease, the acute abdomen, and radiological evaluation of bone tumors. In addition, studies have been performed in the areas of thyroid disease[1] and the diagnosis of Cushing's syndrome.[2]

Although the area of congenital heart disease was well studied by Warner, Veasy and Toronto, their diagnostic model involved patients ranging in age from one month to twenty years. Another population, those who display their initial symptoms in the period between birth and one month were excluded. A great number of patients with congenital heart disease, particularly those with the most severe disorders, are seen in the neonatal period. More than one-fourth of all infants with congenital heart defects die before the age of one month, most within the first week.[3]

It has been the purpose of this study to apply the techniques of Bayesian analysis to cardiological diagnosis in the newborn period. The area is well suited to a

predictive model: diagnosis is based primarily on physical findings and radiographic and electrocardiographic data rather than the more subjective history. Also, as the majority of patients, other than those with small PDAs and pulmonary disease, are catheterized, clinical diagnoses can be checked by objective data.

Development of a Bayesian statistical model requires a number of steps. One must specify the clinical problem and identify the patient population. Next, one must decide upon the relevant symptoms, physical findings and laboratory, electrocardiographic and radiographic data and prepare a comprehensive list of diseases which occur in the population. The Bayesian system then depends upon completion of the symptom-disease matrix: data about the incidence of each disease within the population, and the occurrence of each symptom within each disease. Using a computer program to tabulate the large quantity of data under consideration, a number of cases must be analyzed to determine the validity of the system.

The clinical problem in this thesis is congenital heart disease in the neonate. The population which has been selected was arbitrarily limited to any patient admitted to the Yale-New Haven Hospital Newborn Special Care Unit. While this may exclude a few neonates admitted to a different hospital unit or in rare cases may include

patients beyond the first month of life, it has been necessary to adhere to these limits since the symptom-disease was constructed with regard to that population. Each of the other components will be discussed in its approach section.

Symptoms

To assess the symptoms relevant to the diagnosis of congenital heart disease, charts of patients evaluated for cardiac disease in the neonatal period were reviewed. Comparing these to the diagnostic workup suggested by Talner and Campbell,[4] it was possible to compile a list of pertinent findings. Historical data included prenatal conditions such as infection, hypertension or drug use, length of gestation, and other family history of congenital abnormalities. On physical exam, in addition to the vital signs, observations were made on the pulse quality (intensity in all extremities), liver size, autonomic activity and skin color. Cardiac exam included evaluation of thrills or heaves, and auscultation for the quality of the first and second heart sound, the presence of gallops or clicks and the location, timing, quality and intensity of murmers. Laboratory evaluation included hemoglobin, hematocrit, acid-base status and blood gases in room air and with increased oxygen tension. A chest roentgenogram permitted evaluation of heart size,

pulmonary vasculature and lung fields, possible chamber
enlargement, and on rare occasions, abnormalities in the
location of abdominal viscera, the heart and the aorta.
Electrocardiographic data included conduction patterns,
chamber hypertrophy, and direction of electrical forces.

Several criteria must be met before these symptoms
can be employed in a statistical model. Limited by
the ability of digital computers to handle only numerical
data, symptoms must be organized into discrete units.
For example, a white count, elevated or normal, or plantar
reflexes, up or down, are distinct possibilities. Find-
ings which fall into subjective categories - for example,
the degree of pain in arthritis - either require special
handling or must be omitted. Modifications might involve
definitions of the gradations. Pain, if strictly defined
into categories of absent, mild, moderate or severe,
represents discrete categores.

Second, if a symptom is to be included, it must
have a known relationship to the diagnosis. For example,
a history of maternal infection other than rubella may
increase the likelihood of congenital heart disease,
but may make no contribution to the specific diagnosis.

Third, definite and consistent criteria must be
established for each variable. Cardiac size is difficult
to assess in the neonatal period. To use such a symptom

requires establishment of specific standards.

Fourth, it is important that data be organized in the form it is obtained. For example, murmurs may be defined as "loud" or "soft" by standardized phono-cardiographic deflection. If a phonocardiogram is not routinely obtained, the significance of loud and soft may be lost.

Finally, one must remember Lusted's admonition to avoid related symptoms. If arterial desaturation is used, cyanosis must be omitted. Desaturation, while not completely correlated with skin color, is both the cause of and highly related to cyanosis.

With the assistance of three experts in neonatal cardiology, Dr. Norman Talner and Dr. Marie Browne of the Department of Pediatrics, and Dr. Allan Simon of the Department of Radiology, it was possible to select the general categories of data which were utilized in the diagnosis of neonatal cardiological disease. For many of the observations, the separation between normal and abnormal was apparent. The location of the aorta, if observed, could only be left or right. A patient could, for all practical purposes, be only male or female. For other observations, particularly those employing quantification as in pulse rate, oxygen saturation, etc., it was necessary to establish cut-offs

between normal and abnormal. Upon examination of a
large number of charts, it became apparent that certain
groupings of data occurred within each disease and
often these groupings were consistent between diseases.
For example, in examining the data on the age of the
patient at initial presentation, it was readily apparent
that certain diseases manifested early in life - aortic
atresia (hypoplastic left heart), persistent fetal
pathways, and transposition of the great arteries.
Others, such as aortic or pulmonary stenosis, Tetralogy
of Fallot or Ebstein's abnormality, generally presented
later in the newborn period. The age which separated
the early from the late group was approximately three
days of age: while some patients with valvular atresia
presented later in life and others with stenosis presented
earlier, it was possible to separate them best using the
age three days.

For arterial desaturation, three groups of values
were apparent: the lowest values were present in the
transposition complexes, significant desaturation was
present in right to left shunts, and minimal or no desatur-
ation was present in other patients. Limited by the
availability of data, it became necessary to group pO_2
values into only two groups, those with a pO_2 less than
45 and those above. In the absence of blood gas values,

the appearance of generalized cyanosis (not just perioral) was taken to correlate approximately with the lower range of arterial oxygenation, an assumption which could be inaccurate in the face of variations of hemoglobin concentrations.

Certain data, while reported consistently in the charts, was unable to satisfy the criteria established previously. For example, the "quality" of the first heart sound, while consistently noted in the charts, did not lend itself to use. The frontal axis of the p-wave, while frequently noted, was never abnormal, and consequently provided no data base.

The greatest difficulty arose in the selection of criteria for ventricular hypertrophy. Great variation exists in electrocardiographic ventricular patterns during the newborn period. Absolute criteria for hyper-trophy patterns are available in the literature,[5] but are so restrictive that patients documented to have hypertrophy may not satisfy the criteria.[6] To surmount this difficulty, the R to S ratio in V_1 was selected as an indicator of the relative presence of ventricular forces. While patients with an increased or decreased R to S ratio may or may not be considered clinically to have hypertrophy; if the symptom-disease matrix is organized in the identical format rather than in terms of left,

or bi-ventricular hypertrophy, operation of the Bayesian system is not disturbed.

Similar choices were made for each of the other pieces of data. While controversy often arose and certain omissions were necessary - for example, the presence of Down's Syndrome may be very important in suggesting an endocardial cushion defect - the data selected included the majority considered in the clinical diagnosis. Another omission involves the presence of chamber enlargement on chest roentgenogram: a consulting radiologist with experience in neonatal angiography[7] suggested that specific chamber enlargement cannot be ascertained accurately in the newborn period.

Echocardiographic data have also been omitted. While echos may be very valuable in determining the presence of a valve or the size of a chamber, the use of echo-cardiography is not sufficiently standardized, nor is there adequate data available to incorporate it into a study of this kind. Later, as sufficient data is collected, it may be possible to incorporate these findings into a Bayesian model.

To simplify the eventual computations, the symptoms were organized into the format of choices, for example, gestational age was divided into premature or term, the second heart sound as single or split and pulses as normal, increased or decreased. A patient can have only

one of these options, or if the observation was omitted, none.

Disease and Incidence Data

A number of series of congenital heart disease appear in the literature: several quantify consecutive autopsies,[8] others involve catheterization or clinical data.[8] Through these and review of one-hundred ninety charts at Yale New Haven Hospital, it was possible to compile the heart diseases of the newborn period. A complete listing is very extensive, involving numerous combinations of defects, and many rare abnormalities. But, it can be greatly simplified if defects are organized collectively; for example, the presence of TGA (Transposition of the Great Arteries) in association with VSD is not dissimilar from TGA with an atrial septal defect. In both cases, the patients have "Transposition Complexes" and can be grouped together under the diagnosis TGA. Patients with a VSD in association with either an ASD or PDA frequently display symptoms of their predominant shunt, usually at the ventricular level, and are symptomatically not unlike patients with a VSD alone.

The final selection of diseases (Figure 18) reflected several criteria:

1. the disease must represent a specific entity

DISEASES

1. Pulmonary atresia.
2. Pulmonary stenosis.
3. Tricuspid atresia with a VSD.
4. Tricuspid atresia without a VSD.
5. Truncus arteriosus.
6. Tetralogy of Fallot.
7. Ebstein's disease.
8. Patent ductus arteriosus.
9. Ventricular septal defect.
10. Endocardial cushion defect.
11. Transposition of the great arteries.
12. Anomolous pulmonay venous drainage.
13. Coarctation with a VSD.
14. Coarctation of the aorta.
15. Hypoplastic left heart.
16. Aortic stenosis.
17. Normal.
18. Primary pulmonary disease.
19. Persistent fetal pathways.
20. Primary myocardial disease.

FIGURE 18

DISEASES

Figure 10

and if it included two or more diseases the
symptoms within each must be similar (thus,
coarctation of the aorta was separated into
those with and those without a VSD)

2. The incidence of the disease must be sufficient
to permit the accumulation of adequate data -
very rare diseases such as tri-atrial heart
were omitted.

3. where combinations of diseases resulted in a
new entity it had to be included separately -
for example the combination of pulmonary
stenosis with a ventricular defect is the
Tetralogy of Fallot, an entity distinct from
its components.

The list includes two non-cardiac entities. "Primary
pulmonary disease" represents those patients with no
intrinsic cardiac defect whose symptoms, tachypnea,
tachycardia, murmurs or cyanosis, are referrable to a
pulmonary process. In the category "normal" are patients
with neither anatomic cardiac defects nor pulmonary
disease who are evaluated for arrythmias, transient cyanosis
or prematurity. Myocardial disease involves myocardopathies
of metabolic origin or coronary artery abnormalities which
produce myocardial ischemia.

Series from the literature were inappropriate for use as incidence data. Neither autopsy series nor catheterization data correlated exactly with the population under consideration. The most appropriate data was obtained from records maintained by the Section of Pediatric Cardiology. The "Regional Infant Care Program" log included all patients catheterized or autopsied during a several year period and for a brief period, all the patients consulted by the service, whether or not an anatomical diagnosis was ever obtained. Through analysis of these records, it was possible to determine the incidence of each of the defects over a several year period. The incidence of "normal", "primary pulmonary disease" and PDAs, three diagnoses for which patients were frequently not catheterized, was computed from the brief period when all consults were recorded. Data on the remaining disease was tabulated from the complete series of catheteriztion or autopsy patients.

Symptom-Disease Matrix

To complete the symptom-disease matrix, three sources were employed. First, one-hundred ninety charts of patients previously evaluated by the pediatric cardiologists were examined. Second, the literature

was reviewed, but little of data existed in the format required by a Bayesian analysis. The sex distribution - male to female ratio for each disease - varies little between sub-populations and can be abstracted from the literature.[9]   Some data on PR and QRS intervals appeared in a text on electrocardiographic data.[10]   Radiographic data on aortic arch location was readily available from the literature in a format applicable to this study.[11]

The third source was the three clinicians mentioned previously. Data on history and physical findings was obtained from Dr. Talner. Electrocardiographic and ausculatory findings were contributed by Dr. Browne. Radiographic data was provided by Dr. Simon.

With these three sources of data, it was possible to perform the initial crude analyses. Reviewing the one-hundred ninety cases, and comparing each to the three sets of data, a final symptom disease matrix was compiled which appears in Appendix 3 . A casual glance at the data will reveal some apparent errors. Many of the symptom complexes total greater than 100% resulting form the absence of 0.00 as an entry anywhere in the matrix. Instead the value 0.01 or greater is employed as a "default" value for a symptom generally absent from a disease. For others, symptoms felt to be distinct clinically were combined: for example, heart size, while recorded as normal, moderately or markedly

enlarged, is dealt with statistically as normal or enlarged. For other symptoms, all the choices are given an equivalent value - .50 or fifty percent. This reflects the lack of significance of these variables. For example, the presence or absence of a third heart sound may be important to a clinical diagnosis. However, the absence of sufficient data and the difficulty of auscultation of a third heart sound eliminated it as statistically significant. In neonatal cardiology, or in any area of medical diagnosis, the differences between observers may play an important role in diagnosis. For example, the difficulty of the auscultatory exam of a tachycardic newborn may yield spurious data. If the second heart sound is reported as single the clinician is more prone to such diagnoses as valvular atresia, transposition or truncus arteriosus rather than a septal defect or patent ductus. A more careful examination may reveal the presence of two components to that sound, suggesting a different group of diagnoses.

Clinicians could minimize the extent of observer variation and its effect on diagnosis were it not for many studies[12] such as one by Yerushalmy[13] in the area of radiology. A group of physicians were presented with roentgenograms which they were to evaluate for the presence of pulmonary tuberculosis. The interpreters were expected to read the films by their usual criteria;

none were defined. All the clinicians missed approxi-
mately twenty-five percent of the positive films. When
the films were reviewed by the same observers several
months later, the same reader was apt to change his
diagnosis for about one of every five positive cases.

Of particular importance to neonatal cardiological
diagnosis is the evaluation of pulmonary vasculature.
The lung fields could demonstrate a number of patterns
including decreased, normal and increased flow, and
a pattern of "flow-failure" or venous obstruction.
Observers generally classify the vasculature into one
of these categories with such qualifieds as "markedly"
or "upper" or "lower limits". Different clinicians
will review the films, both with and without clinical
data, and make different observations. In Arnois'
study[14] three physicians from a Department of Cardiology
and Radiology, all experienced in congenital cardiac
disease, were shown 128 films on three occasions. The
films were selected so that 32 demonstrated decreased
and 32 increased vascularity, all documented by catheter-
ization; the remaining 64 were normal. The clinicians
were shown the masked lung fields on two occasions;
on the final viewing the masking was removed. "The
great majority of errors was made in differentiating
between normal and decreased vasculature .... In contra-
distinction, the differentiation between normal and

increased vasculature was good. An infrequent but
interesting error consisted in the scoring of decreased
vascularity as increased. It is of particular interest
that this error occurred only in cases of the Tetralogy
of Fallot. The converse - scoring of increased vascu-
lature as decreased - did not occur in this study.
The total number of errors in the group of patients
with pulmonary undervascularity was 136 out of 288
readings or 47 percent."[15]

These data would suggest that differentiation
between normal and decreased flow, while important
clinically, is a difficult radiographic observation.
For the purposes of this study, no attempt has been
made in the data base to employ the distinction. If
a clinician observed decreased flow it is placed in
the category of decreased-normal flow. Similarly,
the distinction between increased flow and "flow-failure"
was difficult and these categories were combined.

The evaluation of murmurs is similarly difficult.
Feinstein, in the Prologue to Clinical Judgment, describes
his encounter with observer variation while directing
a rheumatic fever prophylaxis study:

> Soon after I began this new work, while making
> ward rounds one day, I heard a faint, but
> unequivocal diastolic murmur along the left
> sternal border of a patient in whom no murmurs
> had been noted either by the resident physician

of our hospital or by the physicians who had just referred the patient to us. After I demonstrated the murmur to our resident physician, he agreed that it was there and that he had failed to recognize it.

The correction of the resident's error was a simple event - part of the ordinary daily routine of clinical activities and training. Yet, as I later thought about the event, it assumed greater significance. Since the resident physician and I might have been the only two doctors who were going to listen to this patient's heart at our institution the murmur would have been undetected had I not found it. The patient would have been discharged with the same diagnosis of "no heart disease" with which whe had arrived. If the murmur persisted, it would probably be found at some later date by another auscultator. Since the murmur would never have been cited previously, however, the new auscultator might falsely conclude that the murmur had arisen from insidious scarring of an aortic valve whose damage has previously been clinically imperceptible.

The insidious development of scarring in valves that initially seemed undamaged has long been regarded as a major pathogenetic mechanism in rheumatic heart disease. I began to wonder how many patients might have developed such "scarring" as a fallacy of clinical auscultation. De novo rheumatic heart disease - absent on initial examination of a rheumatic patient and found in another examination some time later - might certainly occur by insidious scarring of a valve, but could also be "created" by iatrogenic mechanisms: the abnormal murmur might have been present on both ausculatory examinations although undetected initially; or it might have been absent on both examinations, but erroneously diagnosed as present on the second. The whole concept of insidious de novo rheumatic scarring seemed to depend on clinical auscultation of the heart, and yet auscultators could sometimes be wrong.[16]

In reviewing charts of patients evaluated for congenital heart disease, it was apparent that murmurs were recorded differently by different observers. Beyond

the highly subjective grading of loudness, differences
involve type - holosystolic versus ejection - as well as
location - upper versus lower versus entire sternal
border, for example. Allowance for this type of variation
required significant changes in the matrix. For example,
a left upper sternal border ejection murmur is not
characteristic of a PDA. In several patients in the
series, this was the murmur recorded by the clinician.
If the symptom-disease matrix contained the value 0.00
for the incidence of that murmur with a ductus, Bayes
Law could provide a probability of zero percent for
that diagnosis. To avert this situation, the "default"
value, for each entry is never set at zero, but at least
0.01, unless the presence of a symptom if pathognomonic
of the absence of the disease. The level of the default
value will reflect the vagueness of the symptom.
Murmurs are particularly difficult to evaluate in this
population and ejection murmurs at the left sternal
border are so frequently reported that they are of little
diagnostic significance. Thus, the default value for
ejection murmurs at the left sternal border must be
set high, 0.05, so that their presence eliminates no
diagnoses. Diastolic murmurs are less frequently
recorded so that the default level has been set at two
percent.

Even the evaluation of differential pulses, while more precise, must allow for some observer or disease variation. For several patients in this series, differential pulses were recorded by at least one observer but at catheterization, no cardiovascular abnormality would be demonstrated to explain the finding.

The use of default value increases the total for several symptoms to greater than 1.00. While theoretically impure, this introduces no strain to a Bayesian system. To eliminate the increased totals, one need only normalize the values for each symptom, i.e., divide each entry by the total for that symptom in that disease. In practice, the denominator of Bayes Law acts as a normalizing factor and the use of totals greater than one introduces minimal error to the final diagnosis.

Data Collection

Patient data for the testing of the Bayesian system was collected at three stages. The first group of one-hundred ninety cases were selected from consecutive listings of the Regional Infant Care Program. The second group, fifty patients, was obtained by further review of these listings. An additional thirty charts were requested for these two samples but were not included in the study. In several cases, the patient expired either prior to arrival at the hospital or before

a complete evaluation by the hospital staff. For the
remainder, the charts were unobtainable. Some had
been lost, while others had been signed out to hospital
staff as long as six months earlier and never returned.
The diagnoses of these patients were obtained from the
files of the Section of Pediatric Cardiology. As the
distribution of diagnoses was similar to that of the
remainder of the population, it was felt that omission
of these patients would not compromise the study.

The charts of the patients were abstracted into a
form similar to the one shown in Appendix 1 . If
available, the evaluation by the most senior cardiologist
who saw the patient prior to catheterization was employed.
In the few cases where the cardiologists did not enter
a complete note prior to catheterization or death, the
most senior housestaff's evaluation was used. If in the
chart or the files maintained by the cardiologists, the
electrocardiogram was observed for the pertinent findings.
When absent, this information was obtained from the
clinician's note. In some cases, the clinicians reported
only the QRS axis and ventricular patterns so that data
on PR and QRS intervals was omitted from the analysis.
Approximately half of the chest roentgenograms were
reviewed by the author with assistance from Dr. Simon.
For those films which were unobtainable, the clinician's

observations were employed.

Greater than ninety percent of these patients had undergone catheterization so anatomical diagnoses were generally available. For those patients not cathed, clinical diagnoses were recorded. It is significant to note that these patients represent a sub-grouping of the population under consideration. Since the majority had been catheterized, the sample is skewed towards the more serious defects requiring diagnostic study, and away from the patients with PDAs or other less serious heart defects.

Computer Program

The large number of calculations required by Bayes Law would discourage the user from performing the analysis manually. Through the use of a digital computer, the several thousand logical and mathematical steps can be performed in seconds and at minimal cost. The programming for this research was performed at the Yale Computer Center. Except for some initial data manipulation employing SPSS (Statistical Package for the Social Sciences[17]), all programming was in the Fortran IV Language,[18] an IBM package for the manipulation of numberical data. Computations were performed on the IBM 370/158 using data card input and printed output.

The cost of the program is minimal. Using the most comprehensive output format, a "run" averages $0.80. Of this, $0.25 is a fixed "job charge" and approximately $0.45 is spent reading the input deck and the symptom-disease matrix. Less than $0.10 is actually spent reading in the patient symptom information, performing the thousands of logical and mathematical computations, and printing the output. The cost of reading the deck and matrix could be decreased through the use of binary input. Even the use of an on-line, interactive program would probably amount to less than $1.00 per day.

The program involves three steps. First, the symptom-disease matrix is read into the computer, followed by data on one or more patients. Next, the computations are performed using Bayes Law. The results - the probability of each of the twenty diseases occurring with the given set of symptoms - are then printed.

The actual progarm is shown in Appendix . The majority of steps are either input-output instructions or "book-keeping", i.e., instructions which are necessary only to the computer program and have no bearing on the actual Bayesian analysis. The remainder of the program consists of the instructions for the calculations of Bayes Law. As shown in Chapter III, Bayes Law, with the

assumption of conditional independence of variables, can be written as:

$$P(D_i/S_1,\bar{S}_2,\ldots,S_n) = \frac{P(D_i)P(S_1/D_i)(1-P(S_2/D_i))\ldots P(S_n/D_i)}{\begin{array}{l}P(D_1)P(S_1/D_1)(1-P(S_2/D_1))\ldots P(S_n/D_1) + \\[4pt] P(D_2)P(S_1/D_2)(1-P(S_2/D_2))\ldots P(S_n/D_2)+\ldots+ \\[4pt] P(D_m)P(S_1/D_m)(1-P(S_2/D_m))\ldots P(S_n/D_m)\end{array}}$$

Since the symptoms and the symptom-disease matrix were organized into choices, $\bar{S}_j$ (symptom S_j being absent) would not occur. Instead, some other symptom, possibly S_{j+1} or S_{j-1}, would correspond to the absence of symptom S_j. Bayes Law now reverts to:

$$P(D_i/S_1,S_3,\ldots,S_n) = \frac{P(D_i)P(S_1/D_i)P(S_3/D_1)\ldots P(S_n/D_i)}{\begin{array}{l}P(D_1)P(S_1/D_1)P(S_3/D_1)\ldots P(S_n/D_1) + \\[4pt] P(D_2)P(S_1/D_2)P(S_3/D_2)\ldots P(S_n/D_2) +\ldots+ \\[4pt] P(D_m)P(S_1/D_m)P(S_3/D_m)\ldots P(S_n/D_m)\end{array}}$$

As noted in previous sections, the matrix is in the form of probabilities, while the data on each patient or case is in the form of ones or zeroes, i.e., the patient either has or does not have the symptom. To determine the probability of each disease, one needs to calculate both the numerator and denominator. Fortunately, the denominator is identical for every disease for a given patient, and is in fact, the sum of all the numerators. A great savings

is accomplished by calculating each of the twenty
numerators separately, finding their total and dividing
each by the total. This yields results in the form
of probabilities. To express the results as percentages,
each probability is multiplied by one hundred percent.

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CHAPTER   V

RESULTS AND DISCUSSION

Of the three populations studied, the first (190
patients) was employed in the construction of the symptom-
disease matrix so evaluation of their results would be
inappropriate. The matrix had been constructed previous
to the analysis of the second group (50 patients) so a
statistical evaluation, while fraught with the difficul-
ties present in any retrospective chart review, is
valuable. The third population, the twenty patients
evaluated prospectively, represents the "target" popula-
tion. While small in number, this is the ideal group
for statistical review.

The data analysis for each patient was printed
in a format similar to the one shown in Appendix 4. The
clinical (pre-catheterization) diagnosis is printed along
with the computer's "predicted-diagnosis" and a differential,
any diagnosis which received greater than a one percent
probability in the Bayesian analysis. The choice of
one percent as the limit for a diagnosis to be considered
significant was an arbitrary one arrived at after review
of the initial one-hundred ninety patients. With knowledge
of the operation of a Bayesian system, one learns that

simple shifts in the data base can produce significant changes in the predicted likelihood for any individual disease. Ignoring a diagnosis with a probability of 1.5% could limit the value of a Bayesian analysis, a program which does not "diagnose" a clinical situation, but rather predicts the likelihood of the given set of symptoms in each of the disease under consideration. Theoretically, a situation could arise in which each of the twenty diseases could enter into the differential diagnosis with a probability of greater than one percent, and the Bayesian analysis would have done little to clarify the diagnostic situation. In practice, the differential diagnosis generally approximates five diseases, on occasion it was as large as nine and in several instances only one diagnosis received greater than a one percent probability.

In reviewing the data for the original cases, an additional problem became apparent. The analysis had difficulty differentiating the categories normal and primary pulmonary disease. This reflects the similarity of data for the two categories. In addition, the majority of patients who are diagnosed as normal are evaluated for tachypnea or cyanosis, both of which, if non-cardiac, are most likely of pulmonary origin. The inability of the program to differentiate these categories has required that they be combined. The new category is entitled

"non-cardiac disease". Data provided in the analyses consists of the total of the two separate categories rather than a separate entity.

For the fifty patients studied retrospectively, the Bayesian "predicted diagnosis" agreed with the catheterization or final clinical diagnosis in fifty-two percent. For nine (18%), the clinical diagnosis received the second greatest percentage in the analysis, and for an additional three (6%), the clinical diagnosis corresponded to the third most likley computer diagnosis. In almost ninety percent of the cases, the clinical diagnosis was listed in the computer's differential diagnosis, i.e., in only twelve percent of the cases did the actual diagnosis receive less than a one percent probability. Employing a more conservative cut-off of two percent would increase the percentage of total omissions to sixteen percent and a highly conservative limit of five percent would increase it to eighteen percent. The distribution of clinical versus predicted diagnoses is shown in Figure 19. Only three of the nineteen diagnoses were predicted far more often than they occurred. Tricuspid atresia with a VSD occurred four times in this series and was predicted six times. Coarctation of the aorta occurred twice and was predicted twice as often. Persistent fetal pathways was present in only one patient but it was predicted in two others.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	Total
PREDICTED																				
1. Pulmonary atresia	3		1								1									5
2. Pulmonary stenosis		1				1	1													3
3. Tricuspid atresia with VSD			1								2					1				4
4. Tricuspid atresia w/o VSD	1																			1
5. Truncus arteriosus									1											1
6. Tetralogy of Fallot											1									1
7. Ebstein's disease																				
8. Patent ductus arteriosus	1					1		6												8
9. Ventricular septal defect								1	4	1										6
10. Endocardial cushion defect																				
11. Transposition	1					1	1				2									5
12. Anomolous pulm. ven. drain.																				0
13. Coarctation with VSD													1							1
14. Coarctation														2						2
15. Hypoplastic left heart															6				1	6
16. Aortic stenosis						1														1
17. Non-cardiac disease						1														1
18. Persistent fetal pathweys						1	1											1		3
19. Myocardial disease																	1			1
	6	1	2	0	0	6	3	7	5	1	6	0	1	2	6	1	1	1	1	50

FIGURE 19

Predicted versus actual diagnosis for 50 retrospective cases.

In contrast, the Tetralogy of Fallot occurred in six patients but was predicted only once. For the remainder, the frequency of clinical and computer diagnoses was similar, within plus or minus one.

For the twenty patients studied prospectively, the Bayesian predicted diagnosis agreed with the final clinical or catheterization diagnosis in sixty percent of the cases. In three cases (15%) the actual diagnosis was given the second greatest percentage by the computer program and in one (5%) the actual diagnosis entered the computer's differential as the third most likely. In only one of the twenty cases was the computer unable to give the appropriate diagnosis the one percent probability required for entry into the differential diagnosis.

This was a premature male (Patient 1, Appendix 4) with certain unusual data not considered by the program. In addition to the abnormal findings of a single second heart sound, an ejection murmur at the left lower sternal border, and left axis deviation, the chest roentgenogram revealed the presence of situs inversus with levocardia, a combination associated with specific abnormalities[1]. Using the clinical data, the program yielded two likely diagnoses, a VSD (38.4%) and a patent ductus (29.8%). On reevaluation of the patient one week later (prior to catheterization) the program suggested either a VSD (35.8%)

or an abnormality of the right ventricular outflow tract
(pulmonary atresia or pulmonary stenosis). In neither
did the analysis yield greater than the one percent
probability for the correct diagnosis - an endocardial
cushion defect.

The second cushion defect in the prospective
series illustrates an omission in the symptom list.
The patient's clinical data, a full-term female with
hepatomegaly, an ejection click, a systolic murmur
at the left sternal border, a northwest electrocardio-
graphic axis, cardiomegaly and increased pulmonary blood
flow, is shown in Appendix 4, patient 2. The predicted
diagnosis, a ventricular septal defect, was considered
five times as likely as the actual diagnosis, an endo-
cardial cushion defect. In addition to the two findings
of increased pulmonary flow and a northwest axis which
were highly suggestive to the clinicians of the actual
diagnosis, the patient also displayed Down's Syndrome,
making the clinicians virtually certain of their diagnosis.
The program, not taking into consideration the presence
of Down's Syndrome and its association with cushion
defects, utilized incidence data which penalized cushion
defects strongly (0.014 for ECDs and 0.113 for VSDs) and
subsequently was unable to give the appropriate results.

Another error occurred in a full-term male (Patient
3) who was evaluated at birth. Clinically the patient

displayed only tachypnea, but the chest roentgenogram demonstrated borderline cardiomegaly and a venous obstructive pattern. Using the data, the program suggested a patent ductus (50%) and gave the correct diagnosis, non-cardiac disease, less than a two percent probability. Clinically this infant of a diabetic mother displayed no evidence of a ductus other than an abnormal chest roentenogram and the x-ray findings were attributed to the maternal condition. The computer program, lacking appropriate data on infants of diabetic mothers was unable to ascertain the appropriate diagnosis.

For several other patients, the program not only provided the correct diagnosis but gave a differential diagnosis which very much resembled the clinical differential. For Patient 4, a term male with hepatomegaly, cyanosis, normal ausculatory exam and normal chest roentgenogram, the program gave a great likelihood to both non-cardiac disease (68.4%) and persistent fetal pathways (24.4%), the two major components of the clinical differential. The final diagnosis was non-cardiac disease, which agreed with the predicted diagnosis.

Another term male, Patient 5, was noted to have cyanosis, increased pulses, a single second heart sound, an ejection murmur at the left upper sternal border, a normal cardiogram and a chest roentgenogram demonstrating increased heart size and a venous obstructive pattern.

Three diagnoses - a VSD (28.6%), PDA (27.0%) and truncus arteriosus (23.0%) entered prominently into the computer's differential. The clinicians suspected a PDA because of the pulse intensity and apparently briefly considered the other two diagnoses suggested by the computer. At catheterization a truncus was demonstrated.

For another patient, the computer's diagnosis, while incorrect, was similar to the initial clinical impression. A term male, Patient 6, with decreased pulses, cyanosis, two murmurs and a normal chest roentgenogram was considered clinically to have either a myocardial disorder or persistent fetal pathways. The computer strongly suggested persistent fetal pathways (60.7%) and suggested only a slight probability of a cardiomyopathy (2.2%). At catheterization a complex defect was found which fell into the transposition complex, a diagnosis which the computer had given its second greatest probability (19.0%) but had not entered prominently into the clinical diagnosis.

Several additional cases are displayed in Appendix 4. These demonstrate both correct and incorrect predictions by the program.

Further evaluation of the results might include examination of the probabilities yielded by the computer, or to compare them to clinicians' predictions. In Warner's

study,[2] a method was formulated to compare clinicians' predictions to those of the computer. He created a "Diagnostic Performance Index" which is"

$$DPI = \overline{P} \times F$$

where $\overline{P}$ is the mean probability assigned to the correct diagnosis, and F is the fraction of cases in which the correct diagnosis was given probability greater than one percent. As his clinicians organized their differential diagnosis lists in a format similar to that of the computer, including estimating probabilities, Warner was able to provide meaningful comparisons between clinical and computer diagnoses. In the present study, the clinicians did not estimate probabilities for their predicted diagnoses, and rarely discussed the relative likelihood of different elements of their differential. Thus, it is difficult to make statistical comparisons between the clinician and computer.

In addition, it is important to not place too great a value on the actual probabilities suggested by the computer program. For example, one patient in the retrospective series, a premature female (Patient 12) with normal pulses, a holosystolic murmur at the left lower sternal border, cardiomegaly and increased pulmonary

flow was felt clinically to have a ventricular septal defect. Two diagnoses, a PDA (49.7%) and a VSD (49.4%) entered the computer's differential. At catheterization, a ductus and an intact ventricular septum were demonstrated. To fault the computer for not assigning a greater probability to the appropriate diagnosis would be in error. The program responded to the data it was given by suggesting that two diagnoses - a PDA and VSD - were almost equally likely. In other cases, the low probability assigned to the appropriate diagnosis does not imply that the diagnosis is unlikely, but rather, that other diagnoses must be seriously entertained in the differential. As the number of possible diagnoses increases, the probability assigned to each must necessarily decline.

In spite of the absence of data comparing the clinicians' predictions to those of the computer, some observations can be made. For sixteen of the twenty patients (80%) the clinicians' original diagnosis agreed with their final diagnosis compared to the computer's sixty percent performance. For two patients (10%), the actual diagnosis entered into the clinician's prediction but was not considered to be the most likely diagnosis. For two patients (10%), the actual diagnosis was given a very low probability by the clinicians. In addition,

there were several instances where the clinicians, in examining the computer's complete differential, felt that it was not only more complete, but also more logical, than their own.

Through review of the twenty prospective cases, it has become apparent that there are a number of weaknesses in the data base, the symptom-disease matrix. First, there are great errors in the incidence data. The category "non-cardiac" disease was given only a seven percent incidence in the matrix but was the final diagnosis for thirty-five percent of the patients in the prospective series. This is not surprising: it was known that the retrospective series was heavily skewed towards the more seriously ill patients and included few patients with pulmonary disease or who were normal. The incidence of non-cardiac disease was estimated from data which supposedly included all patients consulted by the service, whether or not catheterization was performed. In retrospect, it is most likely that many patients with non-cardiac disease whose evaluations were minimal were not entered into the Regional Infant Care Program records. Consequently, the incidence data for non-cardiac disease is in error. Similarly, PDAs, a diagnosis which is frequently made without invasive techniques, comprised twenty-five percent of the prospective cases in contrast to 14.7% incidence in the matrix.

Two of the patients in the prospective series had endocardial cushion defects, yielding an incidence seven times that of the symptom-disease matrix. While both these patients were catheterized, it is likely that the diagnosis of a cushion defect is frequently made without catheterization. In patients with Down's Syndrome and a northwest electrocardiographic axis, the diagnosis may be readily apparent. The presence of Down's Syndrome may therefore serve as a contraindication to aggressive diagnostic study. Alternatively, in a larger series of prospective cases, no additional endocardial cushion defects might appear and the incidence data could more closely approximate that of the matrix.

The incidence of many of the remaining diagnoses did not coincide with the predictions. There was only one ventricular septal defect (5%) compared to an incidence figure of 11.3%, and two transposition complexes (10%) compared to a prediction of 18.9%. Hypoplastic left heart never entered the prospective series, while it was predicted to have a 9.9% incidence in the matrix. Several possibilities exist to explain these variations. First, the distribution of congenital heart disease may be shifting due to changing patterns of pre-natal care or abortions. Second, it is difficult to make statistically valid observations of the distribution of nineteen disease

categories in twenty cases. It is also interesting
to note that historically, certain diagnoses have occurred
in clusters: following a period when the diagnosis of
hypoplastic left heart was never made, several patients
were noted in rapid succession to have that disease.
The effect of unknown variables, possibly uterine viral
infections or drugs, cannot be ignored in these distri-
bution variations.

To assess the effect of the incorrect incidence
data on the program, the prospective series was reanalyzed
with the incidence data omitted, i.e., giving each
disease an incidence of five percent. The results
were generally better than when the incidence data was
employed. The percentage of correct diagnoses increased
to seventy-five, one diagnosis was assigned the second
greatest probability and one, the third. None of the
differential diagnoses omitted the correct diagnosis.
The lowest probability assigned to the correct diagnosis
was 4.1%. By omitting the incidence data from the
analysis, although one is violating Bayes Law, the analysis
yields the comparison of the patient's symptoms to those
present in each disease, ignoring the relative frequency
of each disease. In two cases described previously,
this variation yielded interesting results shown in
Appendix 5. The predicted diagnosis for Patient 5

became truncus (77.7%) which was the catheterization diagnosis. Patient 2 was appropriately diagnosed as having an endocardial cushion defect (29.6%). For several of the patients, those with diagnoses of transposition or PDA, this variation decreased the probability assigned to the correct diagnosis, but in none of these cases did it change its location in the differential diagnosis. These observations would suggest two possibilities. First, the incidence data for the program contains serious errors which should be revised before the program can be used effectively. Second, they suggest that a variation of Bayes Law:

$$P(D/S) \quad \propto \quad P(S/D)$$

may have statistical significance. This formula is equivalent to the observation that a disease is more likely if the symptoms which are present resemble those likely in the disease, even if the disease is known to occur rarely. This is similar to the clinician making his diagnosis in the absence of incidence data, or employing incidence data in crude forms such as rare, frequent, etc. An error potentially introduced by this variation might be to overdiagnose rare diseases.

Other errors have also become apparent during the testing of the matrix. For example, the occurrence of decreased pulses in Ebstein's disease was set at the

default level. Subsequently, it has become apparent
to the author that decreased pulses are probably common
in Ebstein's disease and the value should be set higher.
The data on the distribution of murmurs similarly
contains errors. Ejection murmurs at the left upper
sternal border were frequently reported. In many cases,
the computer employed this to give a disproportionately
high value to aortic stenosis. Although ejections
murmurs at that location are consistent with aortic
stenosis, the data must be changed to accomodate the
frequency with which that murmur is reported in associa-
tion with other diagnoses. Other errors in electrocardio-
graphic data, and roentgenographic findings have become
apparent and are being revised for further testing of
this program. One piece of data, the occurrence of
cyanosis in the "non-cardiac disease" population was
surprisingly accurate. Initially, the probability was
set at seventy-five and sixty percent for the "normal",
"primary pulmonary disease" populations respectively.
In the prospective series, of the seven patients in the
"non-cardiac" category, four displayed cyanosis.

A third group of errors involves the omission of
valuable entries from the symptom list. As noted, the
omission of Down's Syndrome may create difficulty in the
diagnosis of endocardial cushion defects. With the
collection of appropriate data, it would be possible to

incorporate this finding. Other symptoms originally
included in the program but ignored in the data analyses
are liver size, pulse and respiratory rate, gallops
and ejection sounds and the direction of T in V_1 in
patients four days or older. Each was omitted because
of insufficient data or the observation that data grouped
too closely around the cut-off points. For example,
the respiratory rate in this population is so frequently
reported as seventy per minute that tachypnea appeared
to be of little value as a discriminating factor. As
data is collected prospectivly and a larger data base
is obtained, it will be possible to incorporate each
of these, and possibly other symptoms and signs.

     Finally, errors introduced by the assumption of
independence of variables must be considered. While
this assumption has not yet appeared to influence the
results, errors could theoretically occur. For example,
if the presence of Down's Syndrome is introduced as a
variable, the incidence data is no longer independent.
For patients with Down's Syndrome, there is a distinct
distribution of congenital heart abnormalities,[3]   in
contrast to the rarer occurrence of cushion defects in
the remainder of the population. Findings whose simul-
taneous occurrence have more than a multiplicative
effect on the diagnosis, would similarly defy the assump-

tion of independence. However, as a Bayesian analysis
becomes unwieldly in the absence of this assumption,
it is necessary despite theoretical limitations.

Despite these errors, the program has yielded
results which frequently resemble the actual diagnosis.
Although comparison to the clinician's predictions is
difficult, the program does not appear to be signifi-
cantly less accurate. With the introduction of better
data it may be possible to employ the program as an
effective adjunct to clinical diagnosis. The need for
pediatric cardiologists would not be lessened through
the use of the program. Clinicians are still needed
to make the clinical observations, perform the auscul-
tatory exam, read the roentgenograms, perform the
catheterization, etc. The program is not capable of
recognizing gross inconsistencies in the data. Also,
the computer makes no recommendations regarding therapeutic
intervention, surgery, etc. It is only capable of
predicting the likelihood of diseases from a given set
of symptoms.

FOOTNOTES

1. John Keith, Richard Rowe, Peter Vlad, <u>Heart Disease</u>
    <u>in Infancy and Childhood</u> (New York, Macmillan,
    1968) pp. 557-563.

2. Homer Warner, Alan Toronto, George Veasy, "Experience
    with Bayes Theorem for Computer Diagnosis of
    Congenital Heart Disease" <u>Annals of the New York</u>
    <u>Academy of Science</u> (Volume 115, July 31, 1964)
    pp. 558-567.

3. Keith, <u>Op. Cit.</u>, p. 808-813.

FOOTNOTES

1. John Reich, Richard Rowe, Peter Vitz, Human Behavior in Infancy and Childhood (New York, ..., 1988) pp. 557-583.

2. Homer Warner, Alan Toronto, George ..., "Experience with Bayes Theorem for Computer Diagnosis of Congenital Heart Disease," Annals of the New York Academy of Science, Volume ..., 1964, ... pp. 558-567.

3. Reich, Op. Cit., p. 303-312.

CHAPTER VI

BEYOND BAYES

In the previous two chapters, the methodology
and results of a Bayesian diagnostic model have been
presented. It has been demonstrated that a Bayesian
model is capable, despite the recognized limitations
in the data base, to assemble a differential diagnosis
which is appropriate to the clinical situation, and
often assigns the appropriate diagnosis the greatest
probability. The utility of such a model is great and
a few of the implications are to be presented in this
chapter.

The value as an adjunct to clinical diagnosis is
apparent. The Leeds model for the diagnosis of acute
abdmonial pain has demonstrated that the accuracy of
a Bayesian model can exceed that of clinicians at many
levels of training. Other studies by Warner and Lodwick
have shown that Bayesian models can yield results similar
to skilled clinicians.

The opportunity for a Bayesian model to influence
a skilled clinician in his preparation of a differential
diagnosis must be considered. Warner has noted that the

two clinicians involved in his studies increased their
own diagnostic accuracy markedly during the study. "The
extent to which the improved performance of the physicians
is the result of experience in preparing data for and
receiving feedback from the computer over this period
of time is difficult to evaluate. It is interesting in
this regard that observer (AFT), who improved the most,
had the most direct contact with the computer results
over the period of this study."[1] Alternatively, the
improvement may have resulted from the clinician being
forced to collect a complete data base.

The Leeds group has also applied their data to
teaching situations.[2] Through the use of random
number charts and a desk-top computer, artificial case
histories can be created for which the student can
assemble a differential diagnosis. In light of the
known accuracy of this particular Bayesian model, it
can be instructive to the student to compare his own
diagnosis with the computers. Regretably, the accuracy
of the diagnosis cannot be compared to a real patient,
but "there are isolated occasions (such as when a patient
scheduled for bedside teaching goes home or refuses
permission) when a series of artificial substitutes
might be useful. Indeed, (we) have found our series
quite useful on occasion - not so much for the cases

themselves as for the subsequent discussion with the
students, to whom the concept of 'certainty' in diagnosis
is often new and intriguing."[3]

An important implication of Bayes Law is the
ability to examine components of the diagnostic workup.
Having compiled and tested a symptom disease matrix,
it is possible to omit an individual symptom or finding
from the analysis and determine the effect on diagnosis.
If it is found to have no effect the utility of that
symptom for the diagnosis of that disease is low. A
mathematical approach to this problem proposed by Warner[4]
involves evaluation of the "information content" of a
symptom for a disease. This "may be defined as the
logarithm of the ratio of the probability that symptom x_1
is present or absent in any patient from this population.

$$I = \ln(P(x_1/y_1)/P(x_1))$$

Now this information can be either positive or negative
since the probability of a particular symptom in a
given disease may be greater or less than the incidence
of that symptom in the group of diseases under study.
However, if the information content is defined as the
absolute value of the logarithm of this ratio, a number
is obtained which is independent of the sign of the
measure. The average information content ($\bar{I}$) of a given

symptom for a set of k diseases can be obtained from:

$$\bar{I} = \frac{1}{k} \sum_{all\ k} |\ \ln P(x_1/y_k) - \ln P(x_1)\ |$$

Now since:

$$\frac{P(y_k/x_1)}{P(y_k)} = \frac{P(x_1/y_k)}{P(x_1)} = e^{\bar{I}}$$

..., the term $e^{\bar{I}}$ is the average factor by which the calculated probability of a disease is changed by finding symptom x_1 to be present or absent in the patient to be diagnosed. This term then is a direct measure of the average value of that particular symptom in diagnosing this group of diseases."[5]

Warner proposes three criteria for the inclusion of a symptom in a Bayesian model:[6]

1. A symptom should be one whose presence or absence can be accurately recognized.

2. A symptom should be independent of other symptoms in any given disease.

3. A symptom should have an information content greater than 1.0.

Of these, the third offers the greatest opportunity in the application of Bayes Law to medical diagnosis. Applying these calculations to a clinical problem enables one to determine the information content of

each symptom: those with very low information contents could be omitted from the diagnostic workup. Warner notes that vague symptoms such as fatigue have a low information content in his congenital heart disease model, and these were omitted from subsequent analyses.[7] In a more sophisticated model, the information content of a symptom can be compared to its cost. Those symptoms with a low information content to cost ratio could be omitted. Ultimately, Bayesian analysis offers a technique to structure a medical workup to optimize results while minimizing costs and inconvenience for the patient.

Another use of Bayes Law, in sequential processing and optimization, comes from models offered by Gorry[8] and Ginsberg.[9] In every clinical situation, the clinician proceeds in a sequential manner, collecting initial data, formulating a clinical impression, collecting additional data, revising the differential and so on. "The value of information obtained from a test is determined by the contribution that this information makes to improving the current view and hence reducing the risk of misdiagnosis with its associated cost. The more information the doctor obtains about the patient, on the average, the less risk of a possible misdiagnosis. Hence, the doctor is inclined to perform many tests. On the other hand, the tests available to him are not without

some cost in terms of patient discomfort, time of skilled
persons, money, etc. Thus, there is a conflicting
tendency to hold the number of diagnostic tests to
a minimum."[10]

Gorry, in a reanalysis of the data collected by
Warner, proposes to evaluate a patient for congenital
heart disease in a sequential pattern. The clinician
might observe the age of the patient and check for
cyanosis and murmurs. He may next obtain an EKG or
perhaps he would choose a chest roentgenogram. Gorry
optimizes this decision by determining which single
test is most likely to clarify the diagnostic question.
An initial description of the patient is fed to the
computer and a set of Bayesian probabilities determined.
Then, each of the other symptoms is entered separately
into the program, along with the "cost" of the test
(in this case, all equivalent) and the seriousness of
misdiagnosis for each disease (again, all equivalent in
this case). The test which optimizes the results is
requested and the calculations performed again. When
the introduction of additional information no longer
contributes to the certainty of the diagnosis and the
"cost" of misdiagnosis is minimized, the program termi-
nates. Using sequential processing, the program yields
results statistically comparable to Warner's. Of signifi-

cance is the program's use of fewer than seven tests on the average, compared to the thirty-one required by Warner's initial progarm.

Ginsberg in his decision analysis model for the pleural effusion syndrome, introduces a number of variables which the clinician uses but have been omitted from earlier Bayesian models. The cost of tests, the time delays and risks involved in ordering complex tests or laboratory procedures and the value of further diagnostic intervention are all considered. At each point in the analysis, the program optimizes its decisions. If a lab test or procedure adds little to the diagnosis in light of the present clinical picture, it is not requested by the program. In contrast, any inexpensive but valuable screening procedure such as a tuberculin test, enters early into this type of model. Through the introduction of parameters of cost, risk and time delay in clinical diagnosis, despite the different values placed on these factors by different clinicians, it is possible to expand statistical decision analysis to more complex medical problems.

The role which Bayes' Law and computational devices will play in the future of medical diagnosis depends upon physician acceptance. The opportunities can be well illustrated by an analogy. "The clinician often uses a stethoscope to augment his ability to hear sounds

emanating from within a body cavity. Sometimes the clinical picture is clearcut; in this instance the clinician merely uses his stethoscope to confirm his previous assessment of the patient. Sometimes the results which the clinician obtains from the use of the stethoscope are difficult to interpret or are at odds with what the clinician 'feels' about the case - in such circumstances the clinician is at liberty to dis-regard the evidence from his 'machine'. But in a proportion of cases the evidence the clinician obtains will alter his impression of the case sufficiently to make him seek additional evidence and this in turn will lead him to the correct diagnosis."[11]

So it is with a Bayesian program. By helping to sort through large quantities of data, an area in which physicians are known to be relatively weak[12] , the computer can provide suggestions which may aid the clinician in arriving at the appropriate diagnosis.

FOOTNOTES

1. Homer Warner, Alan Toronto, George Veasy, "Experience with Bayes' Theorem for Computer Diagnosis of Congenital Heart Disease" Annals of the New York Academy of Science (July 31, 1964, Vol. 115, pp. 566-567.

2. F. T. deDombal, Jane Horrocks, et al., "Production of Artificial 'Case Histories' by Using a Small Computer" British Medical Journal (June 5, 1971, Vol. 2) pp. 576-581.

3. Ibid., p. 580.

4. Homer Warner, "Medical Diagnosis Using a Digital Computer" Proceedings of the Third IBM Medical Symposium (1963) pp. 305-317.

5. Ibid., p. 307.

6. Loc. Cit.

7. Alan Toronto, George Veasy, Homer Warner, "Evaluation of a Computer Program for Diagnosis of Congenital Heart Disease" Progress in Cardiovascular Diseases (January, 1963, Vol. 5, No. 4) p. 374.

8. Anthony Gorry, Octo Barnett, "Sequential Diagnosis by Computer" Journal of the American Medical Association (September 16, 1968, Vol. 205, No. 12) pp. 849-854.

9. A. S. Ginsberg, Decision Analysis in Clinical Patient Management with an Application to the Pleural Effusion Syndrome (Santa Monica, Rand Corporation, 1971).

10. Gorry, Op. Cit., p. 850.

11. Jane Horrocks, A. P. McCann. "Computer-Aided Diagnosis: Description of an Adaptable System and Operational Experience with 2034 Cases" British Medical Journal (April 1, 1972, Vol. 2) p. 9.

12. F. T. deDombal, J. C. Horrocks, et al., "Pattern Recognition: A Comparison of the Performance of Clinicians and Non-Clinicians with a Note on the Performance of a Computer Based System" Methods of Information in Medicine (Vol. 11, No. 1, 1972) pp. 32-37.

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APPENDIX l :   Data Collection Form

APPENDIX I : Data Collection Form

CARD #1

UNIT #	_ _ _ _ _ _	(1-6)
GESTATIONAL AGE	37-44 WEEKS 20-36 WEEKS	(9) (10)
AGE AT TIME OF EVALUATION	0-3 DAYS 4-42 DAYS	(11) (12)
SEX	MALE FEMALE	(13) (14)
PULSE RATE	170-250 50 -169	(15) (16)
PULSE INTENSITY	NORMAL INCREASED DECREASED	(17) (18) (19)
DIFFERENTIAL PULSES	ABSENT PRESENT	(20) (21)
LIVER-CM BELOW COSTAL MARGIN	0-2 3-10	(22) (23)
DIFFERENTIAL CYANOSIS	ABSENT PRESENT	(24) (25)
RESPIRATORY RATE	0 -70 71-100	(26) (27)
PO2	0-44 45-100	(28) (29)

(IF BLOOD GASES ARE NOT AVAILABLE, USE GENERALIZED
CYANOSIS AS EQUIVALENT TO PO2 LESS THAN 45)

PO2 INCREASE ON 100% O2	0 -29 30-200	(30) (31)
PH	7.00-7.29 7.30-7.60	(32) (33)
S2	SPLIT SINGLE	(34) (35)
S3	ABSENT PRESENT	(36) (37)
S4	ABSENT PRESENT	(38) (39)
EJECTION SOUNDS	ABSENT PRESENT	(40) (41)
NO SYSTOLIC MURMER NO DIASTOLIC MURMER		(42) (43)
APEX	SYSTOLIC HOLOSYSTOLIC EJECTION DIASTOLIC CONTINUOUS	(44) (45) (46) (47) (48)
LEFT LOWER STERNAL BORDER	SYSTOLIC HOLOSYSTOLIC EJECTION DIASTOLIC CONTINUOUS	(49) (50) (51) (52) (53)
LEFT UPPER STERNAL BORDER	SYSTOLIC HOLOSYSTOLIC EJECTION DIASTOLIC CONTINUOUS	(54) (55) (56) (57) (58)
RIGHT UPPER STERNAL BORDER	SYSTOLIC DIASTOLIC	(59) (60)

CARD #2

PR INTERVAL	0.04-0.11	(8)
	0.12-0.20	(9)
QRS INTERVAL	0.03-0.06	(10)
	0.07-0.15	(11)
QRS AXIS	270-360 OR 0-59	(12)
	60 -180	(13)
	181-269	(14)
R/S IN V1	GREATER THAN 10	(15)
	BETWEEN 0.8 AND 10	(16)
	LESS THAN 0.8	(17)
T IN V1	POSITIVE	(18)
	ZERO OR NEGATIVE	(19)

(OMIT IF PATIENT LESS THAN FOUR DAYS OF AGE)

PULMONARY BLOOD FLOW	NORMAL	(20)
	DECREASED	(21)
	INCREASED W/O VEN. OBST.	(22)
	INCREASED WITH VEN. OBST.	(23)
HEART SIZE	NORMAL	(24)
	MODERATELY INCREASED	(25)
	MARKEDLY INCREASED	(26)
AORTIC ARCH	LEFT	(27)
	RIGHT	(28)

CARD #3

CLINICIAN   __   (8-9)

```
01 - TALNER
02 - BROWNE
03 - NUDEL
04 - BERMAN
05 - HELLENBRAND
06 - GLANZ
07 - RESIDENT
08 -
09 -
10 -
```

DATE   __ /__ /__   (11-18)

MONTH/DATE/YEAR

CLINICAL DIAGNOSIS   __   (20-21)
CATH DIAGNOSIS   __   (23-24)

```
1- PULMONARY ATRESIA
2- PULMONARY STENOSIS
3- TRICSPID ATRESIA WITH VSD
4- TRICUSPID ATRESIA W/O VSD
5- TRUNCUS ARTERIOSUS
6- TETRALOGY OF FALLOT
7- EBSTEINS DISEASE
8- PATENT DUCTUS ARTERIOSUS
9- VENTRICULAR SEPTAL DEFECT
10-ENDOCARDIAL CUSHION DEFECT
11-TRANSPOSITION
12-ANOM.PULM.VEN.DRAINAGE
13-COARCT WITH VSD
14-COARCTATION
15-HYPOPLASTIC LEFT HEART
16-AORTIC STENOSIS
17-NORMAL
18-PRIMARY PULMONARY DISEASE
19-PERSISTENT FETAL PATHWAYS
20-PRIMARY MYOCARDIAL DISEASE
```

APPENDIX 2 :   Computer Program

```
0001              DIMENSION ARRAY(74,20),CASE(74),BAYES(20),PROB(20),DOC(3,10),
                 *DESC(15,74),DIS(11,21),NAME(5)
0002              READ (5,100) (ARRAY(1,J),J=1,20)
0003          100 FORMAT(7X,20F3.3)
0004              DO 99 I=2,74
0005           99 READ(5,98)(ARRAY(I,J),J=1,20)
0006           98 FORMAT(7X,20F3.2)
0007              READ(5,150) DOC
0008          150 FORMAT(5X,3A4)
0009              READ(5,151) DESC
0010          151 FORMAT(5X,15A4)
0011              READ(5,152) DIS
0012          152 FORMAT(5X,11A4)
0013          114 READ(5,101,END=509)LUNIT,CASE,NA,MON,DATE,YEAR,NLDX,NTDX,NAME
0014          101 FORMAT(I6,1X,53F1.0/7X,21F1.0/7X,I2,3(1X,A2),2(1X,I2),1X,5A4)
0015              IF (NLDX.EQ.0) NLDX=21
0016              IF (NTDX.EQ.0) NTDX=21
0017              WRITE(6,500)NAME,LUNIT,(DOC(I,NA),I=1,3),MON,DATE,YEAR
0018          500 FORMAT('1'//' PATIENT:   ',5A4//' UNIT #:   ',I6//' CLINICIAN: DR.
                 * ',3A4// ' DATE:    ',A2,'/',A2,'/',A2//' SYMPTOMS:'/)
0019              DO 501 I=2,74
0020              IF (CASE(I).EQ.0) GO TO 501
0021              WRITE(6,502)(DESC(K,I),K=1,15)
0022          502 FORMAT(5X,15A4)
0023          501 CONTINUE
0024              WRITE(6,701)(DIS(L,NLDX),L=1,11)
0025          701 FORMAT(//' CLINICAL DIAGNOSIS:'//5X,11A4)
0026              WRITE(6,503)
0027          503 FORMAT(//' PREDICTED DIAGNOSIS:'/)
          C IF VARIABLES ARE TO BE OMITTED, CASE( )=0 MUST BE DECLARED NOW.
0028              CASE(1)=1.0
0029              CASE(19)=0.0
0030              CASE(20)=0.0
0031              CASE(29)=0.0
0032              CASE(30)=0.0
0033              CASE(33)=0.0
0034              CASE(34)=0.0
0035              CASE(64)=0.0
0036              CASE(65)=0.0
0037              TOTAL=0.0
0038              DO 103 J=1,20
0039              BAYES(J)=1.0
0040              DO 102 I=1,74
0041              IF(CASE(I).EQ.0.0) GO TO 102
0042              BAYES(J)=BAYES(J)*ARRAY(I,J)
0043          102 CONTINUE
0044          103 TOTAL=TOTAL+BAYES(J)
0045              DO 104 J=1,20

0046          104 PROB(J)=100*BAYES(J)/TOTAL
0047              PROB(17)=PROB(17)+PROB(18)
0048              PROB(18)=0.0
0049              K=1
0050              DUMMY=PROB(1)
0051              DO 400 I=2,20
0052              IF (PROB(I).LE.DUMMY) GO TO 400
0053              DUMMY=PROB(I)
0054              K=I
0055          400 CONTINUE
0056              WRITE(6,401)(DIS(L,K),L=1,11),PROB(K)
0057          401 FORMAT(5X,11A4,10X,'(',F4.1,'%)')
0058              PROB(K)=0.0
0059              WRITE(6,504)
0060          504 FORMAT(//' OTHER POSSIBLE DIAGNOSES:'/)
0061              DO 508 M=1,19
0062              K=1
0063              DUMMY=PROB(1)
0064              DO 450 I=2,20
0065              IF (PROB(I).LE.DUMMY) GO TO 450
0066              DUMMY=PROB(I)
0067              K=I
0068          450 CONTINUE
0069              IF (PROB(K).LT.1.0) GO TO 505
0070              WRITE(6,401)(DIS(L,K),L=1,11),PROB(K)
0071          508 PROB(K)=0.0
0072              M=M+1
0073          505 IF (M.NE.1) GO TO 506
0074              WRITE (6,507)
0075          507 FORMAT('    NONE')
0076          506 GO TO 114
0077          509 CONTINUE
0078              END
```

APPENDIX 3 : Symptom-Disease Matrix

APPENDIX 3 : Symptom-Disease Matrix

Note: This page is a dense, sideways computer printout consisting of a numeric data matrix. The row index column is labelled **INC** with rows **1–36**. Reading the table in its normal orientation, each INC row carries a series of probability-like values (0.00–0.99) across the columns.

INC																			
1	0.94	0.94	0.94	0.94	0.94	0.94	0.94	0.74	0.94	0.97	0.97	0.99	0.80	0.40	0.94	0.94	0.94	0.50	0.90
2	0.06	0.05	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.03	0.03	0.11	0.20	0.60	0.06	0.90	0.06	0.50	0.10
3	0.25	0.25	0.75	0.75	0.50	0.25	0.50	0.25	0.50	0.50	0.75	0.10	0.35	0.60	0.25	0.10	0.25	0.50	0.50
4	0.75	0.75	0.25	0.25	0.60	0.75	0.50	0.75	0.50	0.50	0.25	0.40	0.45	0.25	0.75	0.75	0.75	0.50	0.50
5	0.50	0.50	0.50	0.50	0.40	0.25	0.50	0.67	0.50	0.50	0.75	0.50	0.50	0.75	0.60	0.50	0.50	0.50	0.50
6	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.33	0.50	0.50	0.25	0.50	0.50	0.50	0.40	0.50	0.50	0.50	0.50
7	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
8	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.85	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
9	0.96	0.96	0.96	0.96	0.96	0.96	0.95	0.85	0.85	0.39	0.10	0.90	0.80	0.68	0.96	0.25	0.96	0.50	0.49
10	0.02	0.02	0.02	0.02	0.02	0.02	0.10	0.10	0.10	0.01	0.05	0.05	0.10	0.30	0.02	0.01	0.02	0.50	0.01
11	0.02	0.02	0.02	0.02	0.02	0.02	0.05	0.05	0.05	0.10	0.05	0.05	0.10	0.02	0.02	0.74	0.02	0.02	0.50
12	0.99	0.99	0.99	0.99	0.99	0.99	0.50	0.50	0.99	0.99	0.99	0.99	0.99	0.99	0.99	0.99	0.99	0.99	0.99
13	0.01	0.01	0.01	0.01	0.01	0.01	0.50	0.50	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.10	0.01	0.01
14	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
15	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
16	0.99	0.99	0.99	0.99	0.99	0.99	0.85	0.85	0.85	0.99	0.99	0.99	0.99	0.99	0.99	0.85	0.90	0.99	0.99
17	0.01	0.01	0.01	0.01	0.01	0.01	0.15	0.15	0.15	0.01	0.01	0.01	0.01	0.01	0.01	0.15	0.10	0.01	0.01
18	0.35	0.35	0.35	0.35	0.35	0.80	0.75	0.20	0.20	0.20	0.25	0.20	0.20	0.20	0.35	0.20	0.35	0.20	0.35
19	0.65	0.55	0.65	0.65	0.65	0.20	0.25	0.80	0.80	0.80	0.75	0.80	0.80	0.80	0.65	0.80	0.65	0.80	0.65
20	0.25	0.25	0.75	0.75	0.75	0.75	0.90	0.50	0.75	0.70	0.50	0.60	0.60	0.45	0.75	0.10	0.55	0.60	0.55
21	0.75	0.75	0.25	0.25	0.25	0.25	0.10	0.50	0.25	0.30	0.50	0.40	0.40	0.55	0.25	0.90	0.45	0.40	0.45
22	0.50	0.50	0.90	0.90	0.90	0.90	0.90	0.50	0.10	0.90	0.25	0.15	0.15	0.10	0.90	0.75	0.50	0.25	0.50
23	0.50	0.50	0.10	0.10	0.10	0.10	0.10	0.50	0.90	0.10	0.75	0.85	0.85	0.90	0.10	0.25	0.50	0.75	0.50
24	0.15	0.15	0.37	0.37	0.45	0.27	0.12	0.50	0.50	0.50	0.35	0.50	0.50	0.20	0.50	0.10	0.50	0.80	0.40
25	0.85	0.35	0.63	0.63	0.55	0.73	0.98	0.50	0.50	0.50	0.65	0.50	0.50	0.80	0.50	0.90	0.50	0.62	0.60
26	0.75	0.75	0.50	0.50	0.50	0.90	0.80	0.90	0.90	0.60	0.90	0.50	0.50	0.80	0.50	0.10	0.50	0.38	0.90
27	0.25	0.25	0.50	0.50	0.50	0.10	0.20	0.10	0.10	0.40	0.10	0.50	0.20	0.20	0.50	0.90	0.90	0.70	0.10
28	0.35	0.35	0.50	0.35	0.35	0.25	0.25	0.25	0.25	0.90	0.25	0.35	0.25	0.25	0.35	0.25	0.25	0.30	0.35
29	0.65	0.65	0.65	0.65	0.65	0.75	0.75	0.75	0.75	0.10	0.75	0.65	0.75	0.75	0.75	0.75	0.65	0.65	0.65
30	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
31	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
32	0.25	0.25	0.25	0.25	0.25	0.50	0.25	0.25	0.25	0.25	0.50	0.75	0.25	0.25	0.25	0.25	0.25	0.25	0.35
33	0.75	0.75	0.75	0.75	0.75	0.50	0.75	0.75	0.75	0.75	0.50	0.25	0.75	0.75	0.75	0.75	0.75	0.75	0.65
34	0.10	0.10	0.02	0.02	0.02	0.10	0.02	0.30	0.50	0.20	0.02	0.10	0.02	0.20	0.02	0.50	0.02	0.10	0.60
35	0.99	0.99	0.99	0.99	0.99	0.95	0.99	0.99	0.99	0.99	0.90	0.90	0.99	0.99	0.95	0.99	0.99	0.99	0.99
36	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.30	0.25	0.05	0.70	0.25	0.05	0.25	0.30	0.05	0.05	0.05	0.40

37	0.05	0.05	0.05	0.05	0.05	0.70	0.05	0.30	0.15	0.05	0.20	0.05	0.05	0.05	0.05	0.40	0.05	0.05	0.05	0.05	0.05	0.40
38	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.15	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
39	0.02	0.02	0.15	0.80	0.10	0.10	0.02	0.02	0.10	0.40	0.02	0.15	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
40	0.02	0.02	0.80	0.55	0.02	0.02	0.02	0.02	0.02	0.55	0.02	0.80	0.02	0.70	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
41	0.40	0.60	0.05	0.05	0.80	0.80	0.90	0.40	0.20	0.05	0.60	0.05	0.90	0.50	0.20	0.20	0.05	0.70	0.30	0.70	0.05	0.05
42	0.40	0.60	0.05	0.05	0.80	0.80	0.90	0.20	0.20	0.95	0.60	0.95	0.90	0.50	0.20	0.20	0.05	0.30	0.30	0.30	0.05	0.05
43	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.02	0.50	0.05	0.50	0.05	0.25	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
44	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.50	0.02	0.50	0.02	0.25	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
45	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.20	0.02	0.02	0.02	0.02	0.02	0.75	0.10	0.80	0.35	0.05	0.02	0.02	0.40	0.40
46	0.05	0.60	0.40	0.20	0.10	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.25	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
47	0.05	0.05	0.05	0.05	0.05	0.10	0.05	0.05	0.05	0.10	0.05	0.10	0.05	0.80	0.10	0.90	0.35	0.05	0.05	0.05	0.40	0.40
48	0.05	0.60	0.40	0.02	0.60	0.02	0.05	0.05	0.05	0.02	0.02	0.02	0.02	0.20	0.05	0.20	0.02	0.02	0.02	0.02	0.02	0.02
49	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.90	0.02	0.90	0.02	0.02	0.02	0.02	0.02	0.02
50	0.10	0.02	0.02	0.02	0.30	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.07	0.02	0.10	0.02	0.02	0.02	0.02	0.02	0.02
51	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.07	0.02	0.05	0.02	0.02	0.02	0.02	0.02	0.02
52	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.30	0.02	0.80	0.02	0.02	0.02	0.02	0.02	0.02
53	0.20	0.60	0.70	0.20	0.60	0.50	0.20	0.60	0.80	0.10	0.50	0.50	0.60	0.20	0.33	0.80	0.40	0.90	0.40	0.90	0.66	0.60
54	0.80	0.40	0.30	0.80	0.40	0.50	0.80	0.40	0.20	0.90	0.50	0.50	0.40	0.20	0.67	0.20	0.60	0.10	0.60	0.10	0.34	0.40
55	0.75	0.80	0.70	0.70	0.80	0.90	0.70	0.80	0.90	0.10	0.50	0.50	0.50	0.70	0.50	0.50	0.90	0.90	0.90	0.90	0.80	0.35
56	0.25	0.20	0.30	0.30	0.20	0.10	0.30	0.20	0.10	0.90	0.50	0.50	0.50	0.30	0.50	0.50	0.10	0.10	0.10	0.10	0.20	0.65
57	0.70	0.20	0.20	0.85	0.05	0.05	0.25	0.05	0.10	0.05	0.05	0.10	0.10	0.20	0.05	0.20	0.55	0.10	0.05	0.10	0.05	0.10
58	0.25	0.75	0.75	0.10	0.75	0.75	0.65	0.75	0.80	0.80	0.75	0.70	0.70	0.85	0.85	0.60	0.05	0.80	0.75	0.30	0.75	0.85
59	0.05	0.05	0.05	0.05	0.05	0.05	0.20	0.30	0.20	0.20	0.20	0.05	0.10	0.05	0.10	0.05	0.40	0.10	0.20	0.20	0.20	0.05
60	0.05	0.05	0.05	0.05	0.80	0.05	0.50	0.75	0.70	0.55	0.05	0.40	0.40	0.15	0.55	0.40	0.30	0.40	0.70	0.55	0.65	0.30
61	0.10	0.15	0.40	0.55	0.10	0.40	0.40	0.20	0.20	0.40	0.47	0.40	0.55	0.40	0.40	0.55	0.65	0.55	0.20	0.40	0.30	0.60
62	0.85	0.80	0.55	0.05	0.10	0.10	0.10	0.05	0.10	0.10	0.48	0.10	0.05	0.45	0.05	0.05	0.05	0.05	0.10	0.05	0.05	0.10
63	0.20	0.05	0.05	0.95	0.05	0.30	0.05	0.30	0.20	0.30	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.35	0.05	0.30	0.05	0.20
64	0.80	0.95	0.95	0.95	0.95	0.70	0.80	0.70	0.80	0.70	0.95	0.95	0.95	0.95	0.95	0.95	0.95	0.65	0.95	0.70	0.85	0.80
65	0.95	0.50	0.50	0.95	0.90	0.60	0.25	0.60	0.40	0.15	0.95	0.40	0.30	0.80	0.30	0.75	0.05	0.65	0.90	0.90	0.90	0.15
66	0.95	0.50	0.50	0.95	0.90	0.90	0.25	0.90	0.40	0.15	0.95	0.40	0.30	0.80	0.30	0.75	0.05	0.93	0.90	0.90	0.90	0.15
67	0.05	0.50	0.50	0.05	0.05	0.10	0.75	0.10	0.60	0.35	0.05	0.60	0.70	0.20	0.70	0.25	0.05	0.07	0.10	0.10	0.10	0.85
68	0.05	0.50	0.05	0.05	0.05	0.10	0.75	0.10	0.60	0.85	0.05	0.60	0.70	0.20	0.70	0.25	0.95	0.07	0.10	0.10	0.10	0.85
69	0.35	0.05	0.05	0.05	0.80	0.25	0.20	0.25	0.20	0.35	0.05	0.20	0.25	0.80	0.20	0.50	0.10	0.30	0.80	0.80	0.80	0.75
70	0.65	0.95	0.95	0.95	0.20	0.75	0.80	0.75	0.80	0.65	0.95	0.80	0.75	0.20	0.80	0.50	0.90	0.20	0.20	0.20	0.20	0.25
71	0.65	0.95	0.95	0.95	0.70	0.75	0.75	0.75	0.80	0.65	0.95	0.80	0.75	0.20	0.80	0.50	0.90	0.20	0.20	0.20	0.20	0.25
72	0.99	0.85	0.85	0.35	0.99	0.70	0.99	0.70	0.60	0.99	0.99	0.99	0.79	0.99	0.99	0.99	0.99	0.99	0.99	0.99	0.99	0.99
73	0.01	0.15	0.15	0.15	0.01	0.30	0.01	0.30	0.10	0.01	0.01	0.01	0.10	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01

APPENDIX 4 : Sample Patients

PATIENT: 1

CLINICIAN: DR. RESIDENT

DATE: 11/ 6/75

SYMPTOMS:

    LE 36 WEEKS GESTATION ·
    LE 3 DAYS OLD
    MALE
    PULSE RATE GT 170
    NORMAL PULSE INTENSITY
    NO DIFFERENTIAL PULSES
    LIVER LE 2 CM BELOW CM
    NO DIFFERENTIAL CYANOSIS
    RESPIRATORY RATE LE 70
    CYANOSIS
    PH LE 7.29
    S2 SINGLE
    S3 ABSENT
    S4 ABSENT
    EJECTION CLICK PRESENT
    NO DIASTOLIC MURMER
    SYSTOLIC MURMER AT THE LEFT LOWER STERNAL BORDER
    PR INTERVAL LE 0.11
    QRS INTERVAL LE 0.06
    AXIS 270-360 OR 0-59
    R/S IN V1 LE 10 AND GE 0.8
    INCREASED PULMONARY BLOOD FLOW W/O VENOUS OBSTRUCTION
    MODERATELY INCREASED HEART SIZE

CLINICAL DIAGNOSIS:

    ENDOCARDIAL CUSHION DEFECT

FINAL DIAGNOSIS:

    ENDOCARDIAL CUSHION DEFECT

PREDICTED DIAGNOSIS:

    VENTRICULAR SEPTAL DEFECT   (38.4%)

OTHER POSSIBLE DIAGNOSES:

    PATENT DUCTUS ARTERIOSUS   (29.8%)
    TRANSPOSITION OF THE GREAT ARTERIES   (14.0%)
    TRICUSPID ATRESIA WITH VSD   (7.9%)
    COARCTATION WITH A VENT SEPTAL DEFECT   (2.8%)
    HYPOPLASTIC LEFT HEART   (2.4%)
    PULMONARY ATRESIA   (1.6%)
    TRICUSPID ATRESIA WITH INTACT VENT. SEPTUM   (1.5%)

PATIENT: 2

CLINICIAN: DR. GLANZ

DATE: 10/26/75

SYMPTOMS:

    GE 37 WEEKS GESTATION
    GE 4 DAYS OLD
    FEMALE
    PULSE RATE GT 170
    NORMAL PULSE INTENSITY
    NO DIFFERENTIAL PULSES
    LIVER GT 2 CM BELOW CM
    RESPIRATORY RATE GT 70
    NO CYANOSIS
    PH GE 7.30
    S2 SPLIT
    S3 ABSENT
    S4 ABSENT
    EJECTION CLICK PRESENT
    NO DIASTOLIC MURMER
    SYSTOLIC MURMER AT THE LEFT LOWER STEPNAL BORDER
    SYSTOLIC MURMER AT THE LEFT UPPER STERNAL BORDER
    PR INTERVAL LE 0.11
    QRS INTERVAL LE 0.06
    AXIS 181-269
    R/S IN V1 LE 10 AND GE 0.8
    T IN V1 GT 0 IN PATIENT AGE GT 3 DAYS
    INCREASED PULMONARY BLOOD FLOW W/O VENOUS OBSTRUCTION
    MODERATELY INCREASED HEART SIZE
    LEFT AORTIC ARCH

CLINICAL DIAGNOSIS:

    ENDOCARDIAL CUSHION DEFECT

FINAL DIAGNOSIS:

    ENDOCARDIAL CUSHICN DEFECT

PREDICTED DIAGNOSIS:

    VENTRICULAR SEPTAL DEFECT   (51.6%)

OTHER POSSIBLE DIAGNOSES:

    TOTAL ANOMOLOLS PULM VENOUS DRAINAGE   (12.7%)
    PATENT DUCTUS ARTERIOSUS   (10.0%)
    ENDOCARDIAL CUSHION DEFECT   (9.3%)
    PULMONARY STENOSIS   (6.7%)
    COARCTATICN WITH A VENT SEPTAL DEFECT   (3.5%)
    AORTIC STENOSIS   (2.4%)
    TRANSPCSITION OF THE GREAT ARTERIES   (1.4%)

PATIENT: 3

CLINICIAN: DR. MATISOFF

DATE: 15/16/75

SYMPTOMS:

    GE 37 WEEKS GESTATION
    LE 3 DAYS OLD
    FEMALE
    PULSE RATE LE 170
    NORMAL PULSE INTENSITY
    NO DIFFERENTIAL PULSES
    LIVER LE 2 CM BELOW CM
    NO DIFFERENTIAL CYANOSIS
    RESPIRATORY RATE GT 70
    NO CYANOSIS
    PH GE 7.30
    S2 SPLIT
    S3 ABSENT
    S4 ABSENT
    EJECTION CLICK ABSENT
    NO SYSTOLIC MURMER
    NO DIASTOLIC MURMER
    PR INTERVAL LE 0.11
    QRS INTERVAL LE 0.06
    AXIS 60-180
    R/S IN V1 LE 10 AND GE 0.8
    INCREASED PULMONARY BLOOD FLOW WITH VENOUS OBSTRUCTION
    MODERATELY INCREASED HEART SIZE
    LEFT AORTIC ARCH

CLINICAL DIAGNOSIS:

    NON-CARDIAC DISEASE

FINAL DIAGNOSIS:

    NON-CARDIAC DISEASE

PREDICTED DIAGNOSIS:

    PATENT DUCTUS ARTERIOSUS   (50.0%)

OTHER POSSIBLE DIAGNOSES:

    VENTRICULAR SEPTAL DEFECT   (21.9%)
    TOTAL ANOMOLOUS PULM VENOUS DRAINAGE   (12.0%)
    PRIMARY MYOCARDIAL DISEASE   (8.7%)
    TRANSPOSITION OF THE GREAT ARTERIES   (3.6%)
    NON-CARDIAC DISEASE   (1.5%)
    COARCTATION OF THE AORTA   (1.3%)

PATIENT: 4

CLINICIAN: DR. RESIDENT

DATE: 10/23/75

SYMPTOMS:

    GE 37 WEEKS GESTATION
    LE 3 DAYS OLD
    MALE
    PULSE RATE LE 170
    NORMAL PULSE INTENSITY
    NO DIFFERENTIAL PULSES
    LIVER GT 2 CM BELOW CM
    NO DIFFERENTIAL CYANOSIS
    RESPIRATORY RATE GT 70
    CYANOSIS
    PO2 INCREASE WITH 100% O2 GE 30
    PH LE 7.29
    S2 SPLIT
    S3 ABSENT
    S4 ABSENT
    EJECTION CLICK ABSENT
    NO SYSTOLIC MURMER
    NO DIASTOLIC MURMER
    PR INTERVAL LE 0.11
    QRS INTERVAL LE 0.06
    AXIS 60-180
    R/S IN V1 LE 10 AND GE 0.8
    NORMAL PULMONARY BLOOD FLOW
    NORMAL HEART SIZE
    LEFT AORTIC ARCH

CLINICAL DIAGNOSIS:

    NON-CARDIAC DISEASE

FINAL DIAGNOSIS:

    NON-CARDIAC DISEASE

PREDICTED DIAGNOSIS:

    NON-CARDIAC DISEASE   (68.4%)

OTHER POSSIBLE DIAGNOSES:

    PERSISTENT FETAL PATHWAYS   (24.4%)
    COARCTATION OF THE AORTA   (4.1%)
    PRIMARY MYOCARDIAL DISEASE   (1.1%)

PATIENT: 5

CLINICIAN: DR. TALNER

DATE: 11/25/75

SYMPTOMS:

    GE 37 WEEKS GESTATION
    GE 4 DAYS OLD
    MALE
    PULSE RATE LE 170
    INCREASED PULSE INTENSITY
    NO DIFFERENTIAL PULSES
    LIVER LE 2 CM BELOW CM
    NO DIFFERENTIAL CYANOSIS
    RESPIRATORY RATE GT 70
    CYANOSIS
    PO2 INCREASE WITH 100% O2 GE 30
    PH GE 7.30
    S2 SINGLE
    S3 ABSENT
    S4 ABSENT
    EJECTION CLICK ABSENT
    NO DIASTOLIC MURMER
    EJECTION MURMER AT THE LEFT UPPER STERNAL BORDER
    PR INTERVAL LE 0.11
    QRS INTERVAL LE 0.06
    AXIS 60-180
    R/S IN V1 LE 10 AND GE 0.8
    T IN V1 LE 0 IN PATIENT AGE GT 3 DAYS
    INCREASED PULMONARY BLOOD FLOW WITH VENOUS OBSTRUCTION
    MARKEDLY INCREASED HEART SIZE
    LEFT AORTIC ARCH

CLINICAL DIAGNOSIS:

    PATENT DUCTUS ARTERIOSUS

FINAL DIAGNOSIS:

    TRUNCUS ARTERIOSUS

PREDICTED DIAGNOSIS:

    VENTRICULAR SEPTAL DEFECT   (28.6%)

OTHER POSSIBLE DIAGNOSES:

    PATENT DUCTUS ARTERIOSUS   (27.0%)
    TRUNCUS ARTERIOSUS   (23.6%)
    TRANSPOSITION OF THE GREAT ARTERIES   (10.7%)
    COARCTATION OF THE AORTA   (6.6%)
    HYPOPLASTIC LEFT HEART   (1.5%)

PATIENT: 6

CLINICIAN: DR. NUDEL

DATE: 12/24/75

SYMPTOMS:

    GE 37 WEEKS GESTATION
    LE 3 DAYS OLD
    MALE
    PULSE RATE LE 170
    DECREASED PULSE INTENSITY
    NO DIFFERENTIAL PULSES
    LIVER LE 2 CM BELOW CM
    NO DIFFERENTIAL CYANOSIS
    RESPIRATORY RATE LE 70
    CYANOSIS
    PO2 INCREASE WITH 100% O2 LT 30
    S2 SPLIT
    S3 PRESENT
    S4 ABSENT
    EJECTION CLICK ABSENT
    NO DIASTOLIC MURMER
    HOLOSYSTOLIC MURMER AT THE LEFT LOWER STERNAL BORDER
    EJECTION MURMER AT THE LEFT UPPER STERNAL BORDER
    QRS INTERVAL LE 0.06
    AXIS 60-180
    R/S IN V1 LE 10 AND GE 0.8
    NORMAL PULMONARY BLOOD FLOW
    NORMAL HEART SIZE
    LEFT AORTIC ARCH

CLINICAL DIAGNOSIS:

    PRIMARY MYOCARDIAL DISEASE

FINAL DIAGNOSIS:

    TRANSPOSITION OF THE GREAT ARTERIES

PREDICTED DIAGNOSIS:

    PERSISTENT FETAL PATHWAYS   (60.7%)

OTHER POSSIBLE DIAGNOSES:

    TRANSPOSITION OF THE GREAT ARTERIES.   (19.0%)
    NON-CARDIAC DISEASE   (10.4%)
    HYPOPLASTIC LEFT HEART   (2.5%)
    PRIMARY MYOCARDIAL DISEASE   (2.2%)
    PULMONARY STENOSIS   (1.8%)
    VENTRICULAR SEPTAL DEFECT   (1.4%)

PATIENT: 7

CLINICIAN: DR. MATISOFF

DATE: 12/21/75

SYMPTOMS:

    LE 36 WEEKS GESTATION
    GE 4 DAYS OLD
    FEMALE
    PULSE RATE LE 170
    INCREASED PULSE INTENSITY
    NO DIFFERENTIAL PULSES
    LIVER LE 2 CM BELOW CM
    RESPIRATORY RATE LE 70
    NO CYANOSIS
    PH GE 7.30
    S2 SPLIT
    S3 ABSENT
    S4 ABSENT
    EJECTION CLICK ABSENT
    CONTINOUS MURMER AT THE LEFT LOWER STERNAL BORDER
    CONTINOUS MURMER AT THE LEFT UPPER STERNAL BORDER
    PR INTERVAL GT 0.11
    QRS INTERVAL LE 0.06
    AXIS 60-180
    R/S IN V1 LE 10 AND GE 0.8
    NORMAL PULMONARY BLOOD FLOW
    NORMAL HEART SIZE
    LEFT AORTIC ARCH

CLINICAL DIAGNOSIS:

    PATENT DUCTUS ARTERIOSUS

FINAL DIAGNOSIS:

    PATENT DUCTUS ARTERIOSUS

PREDICTED DIAGNOSIS:

    PATENT DUCTUS ARTERIOSUS   (98.8%)

OTHER POSSIBLE DIAGNOSES:

    NONE

PATIENT: 8

CLINICIAN: DR. GLANZ

DATE: 12/10/75

SYMPTOMS:

    GE 37 WEEKS GESTATION
    LE 3 DAYS OLD
    MALE
    PULSE RATE LE 170
    NORMAL PULSE INTENSITY
    NO DIFFERENTIAL PULSES
    LIVER LE 2 CM BELOW CM
    RESPIRATORY RATE LE 70
    CYANOSIS
    PO2 INCREASE WITH 100% O2 GE 30
    PH GE 7.30
    S2 SINGLE
    S3 ABSENT
    S4 ABSENT
    EJECTION CLICK ABSENT
    NO DIASTOLIC MURMER
    HOLOSYSTOLIC MURMER AT THE LEFT LOWER STERNAL BORDER
    EJECTION MURMER AT THE LEFT UPPER STERNAL BORDER
    PR INTERVAL LE 0.11
    QRS INTERVAL GT 0.06
    AXIS 181-269
    R/S IN V1 GT 10
    INCREASED PULMONARY BLOOD FLOW WITH VENOUS OBSTRUCTION
    MODERATELY INCREASED HEART SIZE

CLINICAL DIAGNOSIS:

    TRANSPOSITION OF THE GREAT ARTERIES

FINAL DIAGNOSIS:

    TRANSPOSITION OF THE GREAT ARTERIES

PREDICTED DIAGNOSIS:

    TRANSPOSITION OF THE GREAT ARTERIES   (86.6%)

OTHER POSSIBLE DIAGNOSES:

    VENTRICULAR SEPTAL DEFECT   (5.8%)
    HYPOPLASTIC LEFT HEART   (4.0%)
    TRUNCUS ARTERIOSUS   (1.9%)

PATIENT: 9

CLINICIAN: DR. RESIDENT

DATE: 11/17/75

SYMPTOMS:

    GE 37 WEEKS GESTATION
    LE 3 DAYS OLD
    MALE
    PULSE RATE LE 170
    NORMAL PULSE INTENSITY
    DIFFERENTIAL PULSES
    LIVER LE 2 CM BELOW CM
    NO DIFFERENTIAL CYANOSIS
    RESPIRATORY RATE GT 70
    NO CYANOSIS
    PH GE 7.30
    S2 SPLIT
    S3 PRESENT
    S4 ABSENT
    EJECTION CLICK ABSENT
    NO DIASTOLIC MURMER
    SYSTOLIC MURMER AT THE LEFT LOWER STERNAL BORDER
    PR INTERVAL LE 0.11
    QRS INTERVAL LE 0.06
    AXIS 60-180
    R/S IN V1 LE 10 AND GE 0.8
    T IN V1 GT 0 IN PATIENT AGE GT 3 DAYS
    NORMAL PULMONARY BLOOD FLOW
    MODERATELY INCREASED HEART SIZE
    LEFT AORTIC ARCH

CLINICAL DIAGNOSIS:

    COARCTATION WITH A VENT SEPTAL DEFECT

FINAL DIAGNOSIS:

    COARCTATION WITH A VENT SEPTAL DEFECT

PREDICTED DIAGNOSIS:

    COARCTATION WITH A VENT SEPTAL DEFECT   (49.1%)

OTHER POSSIBLE DIAGNOSES:

    COARCTATION OF THE AORTA   (24.3%)
    VENTRICULAR SEPTAL DEFECT   (15.7%)
    AORTIC STENOSIS   (5.0%)
    PATENT DUCTUS ARTERIOSUS   (4.1%)

PATIENT: 10

CLINICIAN: DR. RESIDENT

DATE: 9/30/75

SYMPTOMS:

    LE 36 WEEKS GESTATION
    GE 4 DAYS OLD
    FEMALE
    PULSE RATE LE 170
    NORMAL PULSE INTENSITY
    NO DIFFERENTIAL PULSES
    LIVER LE 2 CM BELOW CM
    RESPIRATORY RATE GT 70
    NO CYANOSIS
    PH GE 7.30
    S2 SPLIT
    S3 ABSENT
    S4 ABSENT
    EJECTION CLICK ABSENT
    CONTINUOUS MURMER AT THE APEX
    CONTINOUS MURMER AT THE LEFT LOWER STERNAL BORDER
    CONTINOUS MURMER AT THE LEFT UPPER STERNAL BORDER
    PR INTERVAL LE 0.11
    QRS INTERVAL LE 0.06
    AXIS 60-180
    R/S IN V1 LT 0.8
    T IN V1 GT 0 IN PATIENT AGE GT 3 DAYS
    INCREASED PULMONARY BLOOD FLOW W/O VENOUS OBSTRUCTION
    NORMAL HEART SIZE
    LEFT AORTIC ARCH

CLINICAL DIAGNOSIS:

    PATENT DUCTUS ARTERIOSUS

FINAL DIAGNOSIS:

    PATENT DUCTUS ARTERIOSUS

PREDICTED DIAGNOSIS:

    PATENT DUCTUS ARTERIOSUS   (97.0%)

OTHER POSSIBLE DIAGNOSES:

    VENTRICULAR SEPTAL DEFECT   (1.5%)

PATIENT: 11

CLINICIAN: DR. NUDEL

DATE: 12/28/75

SYMPTOMS:

    GE 37 WEEKS GESTATION
    LE 3 DAYS OLD
    FEMALE
    PULSE RATE LE 170
    NORMAL PULSE INTENSITY
    NO DIFFERENTIAL PULSES
    LIVER LE 2 CM BELOW CM
    NO DIFFERENTIAL CYANOSIS
    RESPIRATORY RATE LE 70
    CYANOSIS
    PO2 INCREASE WITH 100% O2 LT 30
    PH GE 7.30
    S2 SPLIT
    S3 ABSENT
    S4 ABSENT
    EJECTION CLICK ABSENT
    NO SYSTOLIC MURMER
    NO DIASTOLIC MURMER
    PR INTERVAL LE 0.11
    QRS INTERVAL LE 0.06
    AXIS 181-269
    R/S IN V1 LE 10 AND GE 0.8
    NORMAL PULMONARY BLOOD FLOW
    MODERATELY INCREASED HEART SIZE
    LEFT AORTIC ARCH

CLINICAL DIAGNOSIS:

    NON-CARDIAC DISEASE

FINAL DIAGNOSIS:

    NON-CARDIAC DISEASE

PREDICTED DIAGNOSIS:

    TRANSPOSITION OF THE GREAT ARTERIES   (35.1%)

OTHER POSSIBLE DIAGNOSES:

    NON-CARDIAC DISEASE   (30.7%)
    PERSISTENT FETAL PATHWAYS   (16.9%)
    TOTAL ANOMOLOUS PULM VENOUS DRAINAGE   (11.5%)
    PATENT DUCTUS ARTERIOSUS   (1.6%)
    VENTRICULAR SEPTAL DEFECT   (1.1%)

PATIENT: 12

CLINICIAN: DR.

DATE: 00/00/00

SYMPTOMS:

    LE 36 WEEKS GESTATION
    GE 4 DAYS OLD
    FEMALE
    PULSE RATE LE 170
    NORMAL PULSE INTENSITY
    NO DIFFERENTIAL PULSES
    LIVER LE 2 CM BELOW CM
    NO DIFFERENTIAL CYANOSIS
    RESPIRATORY RATE LE 70
    CYANOSIS
    PH GE 7.30
    S2 SPLIT
    S3 ABSENT
    S4 ABSENT
    EJECTION CLICK ABSENT
    NO DIASTOLIC MURMER
    HOLOSYSTOLIC MURMER AT THE LEFT LOWER STERNAL BORDER
    PR INTERVAL LE 0.11
    QRS INTERVAL LE 0.06
    AXIS 60-180
    R/S IN V1 LE 10 AND GE 0.8
    T IN V1 LE 0 IN PATIENT AGE GT 3 DAYS
    INCREASED PULMONARY BLOOD FLOW W/O VENOUS OBSTRUCTION
    MODERATELY INCREASED HEART SIZE
    LEFT AORTIC ARCH

CLINICAL DIAGNOSIS:

    VENTRICULAR SEPTAL DEFECT

FINAL DIAGNOSIS:

    PATENT DUCTUS ARTERIOSUS

PREDICTED DIAGNOSIS:

    PATENT DUCTUS ARTERIOSUS   (49.7%)

OTHER POSSIBLE DIAGNOSES:

    VENTRICULAR SEPTAL DEFECT   (49.4%)

APPENDIX 5 : Sample Patients-Reanalyzed with
                Incidence Data Omitted

PATIENT: 2

CLINICIAN: DR. GLANZ

DATE: 10/26/75

SYMPTOMS:

    GE 37 WEEKS GESTATION
    GE 4 DAYS OLD
    FEMALE
    PULSE RATE GT 170
    NORMAL PULSE INTENSITY
    NO DIFFERENTIAL PULSES
    LIVER GT 2 CM BELOW CM
    RESPIRATORY RATE GT 70
    NO CYANOSIS
    PH GE 7.30
    S2 SPLIT
    S3 ABSENT
    S4 ABSENT
    EJECTION CLICK PRESENT
    NO DIASTOLIC MURMER
    SYSTOLIC MURMER AT THE LEFT LOWER STERNAL BORDER
    SYSTOLIC MURMER AT THE LEFT UPPER STERNAL BORDER
    PR INTERVAL LE 0.11
    QRS INTERVAL LE 0.06
    AXIS 181-269
    P/S IN V1 LE 10 AND GE 0.8
    T IN V1 GT 0 IN PATIENT AGE GT 3 DAYS
    INCREASED PULMONARY BLOOD FLOW W/O VENOUS OBSTRUCTION
    MODERATELY INCREASED HEART SIZE
    LEFT AORTIC ARCH

CLINICAL DIAGNOSIS:

    ENDOCARDIAL CUSHION DEFECT

FINAL DIAGNOSIS:

    ENDOCARDIAL CUSHION DEFECT

PREDICTED DIAGNOSIS:

    ENDOCARDIAL CUSHION DEFECT   (29.6%)

OTHER POSSIBLE DIAGNOSES:

    VENTRICULAR SEPTAL DEFECT   (20.4%)
    TOTAL ANOMOLOUS PULM VENOUS DRAINAGE   (14.9%)
    COARCTATION WITH A VENT SEPTAL DEFECT   (11.2%)
    AORTIC STENOSIS   (7.7%)
    PULMONARY STENOSIS   (6.4%)
    TRICUSPID ATRESIA WITH VSD   (3.3%)
    PATENT DUCTUS ARTERIOSUS

PATIENT: 5

CLINICIAN: DR. TALNER

DATE: 11/25/75

SYMPTOMS:

    GE 37 WEEKS GESTATION
    GE 4 DAYS OLD
    MALE
    PULSE RATE LE 170
    INCREASED PULSE INTENSITY
    NO DIFFERENTIAL PULSES
    LIVER LE 2 CM BELOW CM
    NO DIFFERENTIAL CYANOSIS
    RESPIRATORY RATE GT 70
    CYANOSIS
    PO2 INCREASE WITH 100% O2 GE 30
    PH GE 7.30
    S2 SINGLE
    S3 ABSENT
    S4 ABSENT
    EJECTION CLICK ABSENT
    NO DIASTOLIC MURMER
    EJECTION MURMER AT THE LEFT UPPER STERNAL BORDER
    PR INTERVAL LE 0.11
    QRS INTERVAL LE 0.06.
    AXIS 60-180
    R/S IN V1 LE 10 AND GE 0.8
    T IN V1 LE 0 IN PATIENT AGE GT 3 DAYS
    INCREASED PULMONARY BLOOD FLOW WITH VENOUS OBSTRUCTION
    MARKEDLY INCREASED HEART SIZE
    LEFT AORTIC ARCH

CLINICAL DIAGNOSIS:

    PATENT DUCTUS ARTERIOSUS

FINAL DIAGNOSIS:

    TRUNCUS ARTERIOSUS

PREDICTED DIAGNOSIS:

    TRUNCUS ARTERIOSUS   (77.8%)

OTHER POSSIBLE DIAGNOSES:

    VENTRICULAR SEPTAL DEFECT   (7.5%)
    PATENT DUCTUS ARTERIOSUS   (5.5%)
    COARCTATION OF THE AORTA   (3.4%)
    TRANSPOSITION OF THE GREAT ARTERIES   (1.7%)
    COARCTATION WITH A VENT SEPTAL DEFECT   (1.1%)

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